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BULLETIN

OF THE NEW YORK ACADEMY OF MEDICINE

Original Articles by

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ANNUAL MEETING ADDRESSES

REPORT ON TRANQUILIZING DRUGS
COMMITTEE ON PUBLIC HEALTH

NEW YORK PATHOLOGICAL SOCIETY

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1. Lockett, S.: Brit. M.J. 2:809 (Apr. 3) 1954.

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2. Wright, W. T., Jr., et al.: J. Kansas M. Soc. 57:410 (July) 1956.

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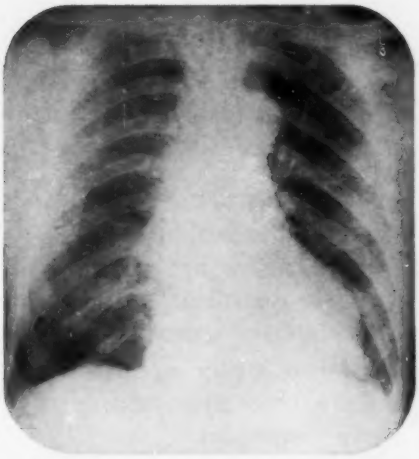

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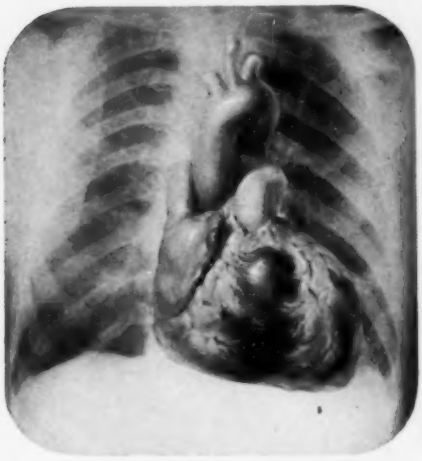

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*Ferrer, F. P., and Boyd, L. J.: Am. J. Dig. Dis., 22:272, 1955
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1. McHardy, G., and Browne, D.: South. M. J. 45:1139, 1952. 2. Hufford, A. R.: Rev. Gastroenterol. 18:588, 1951. 3. Johnston, R. L.: J. Indiana St. M. A. 46:669, 1953. 4. Miller, B. N.: J. South Carolina M. A. 48:345, 1952.

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AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

ROBERT L. CRAIG, *Editor*

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BULLETIN OF
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VOL. 33, NO. 4 APRIL 1957

SPECIALTIES AND MEDICINE*

Inaugural Address

ROBERT L. LEVY

President, The New York Academy of Medicine

On an occasion such as this, the formalities tend to follow a pattern. The retiring veteran, comfortably relaxed by the feeling that he has completed a job well done, puts down his gavel with a sigh of relief; the new recruit takes it up with an enthusiasm born of ignorance, yet keenly aware of the challenge to be met. The Academy exerts a very special and vital influence on the medical life of New York; indeed, it may justly be said that the impact of its activities and deliberations has become national and, through the Bulletin, global. The actual work, upon which rests a reputation for leadership, is done by an able, full-time executive staff and by a number of committees composed of Fellows. The Director is the hub about which the organization revolves and, happily, his guiding force is sustained over a period of years. It has been our good fortune, for the past decade, to have the wise direction of Dr. Howard R. Craig. The President, on the other hand, is a transient. As a member of the Board of Trustees and of the Council, he acts in an advisory capacity and aids in outlining policy and procedure. In

* Delivered at the Annual Meeting of The New York Academy of Medicine, January 3, 1957.

ROBERT L. LEVY, M.D.

accepting this office, I do so with pride in having been chosen and with an earnest desire to carry forward the aims and ideals of many eminent predecessors, at the high level set by them.

At this point I shall deviate from custom in avoiding detailed comment on Academy affairs, of which I still have much to learn. Instead, I propose to reflect briefly on the place of special spheres of activity in medicine. To one who long has wandered in the field of cardiology, this relationship has been of particular interest and concern.

The evolution of specialization was inevitable, largely due to the influence of three factors: first, the development of special skills and techniques; second, the forward surge of knowledge; and third, particularly in recent years, the application of many adjacent sciences to the solution of medical problems. Significant contributions have been made possible with the help of chemistry, physics, engineering, mathematics, statistics and electronics; already the exciting uses of atomic energy have afforded promising glimpses into the future. But how can one person possibly be expected to familiarize himself with all, or even several, of these highly developed disciplines and at the same time become an accomplished clinician? To do so would indeed call for the talents of a superman.

Almost fifty years ago, when Harvey Cushing was actively engaged in establishing neurological surgery on a firm foundation, he wrote as follows: "The specialty is the measure of the man. So long as there are individuals capable, after a general training, of working along novel lines and with the imagination for research which leads to contributions, so long will the field of their endeavors justify its being regarded as special; and it is almost impossible to make definite advances in one direction without permitting other work to go by the board."* A broad, general experience should be part of the education of every physician; it is essential for one who, later in his career, plans to confine his work to a special field.

The core of a specialty is original investigation. In my opinion, regardless of certification by a specialty board, no physician should be content to consider himself a specialist unless he has carried through at least one research problem in his chosen field and has published the results. These need not be of major importance; the approach may be

* Cushing, H. The special field of neurological surgery: five years later, *Bull. Johns Hopkins Hosp. 21*:325-39, 1910.

clinical or by way of one of the basic sciences, or a combination of both. But the experimental method encourages logical thinking and this, together with the judicial weighing of evidence, serves to separate the seed from the husk; in other words, it develops sound scientific critique. Such an attitude leads to valid conclusions, at the bedside as well as in the laboratory.

The desire for scientific advance must not let the whole be obscured by the number and complexity of its parts. There is the danger of concentrating too intently on an area whose boundaries are unduly circumscribed. On this point, Vannevar Bush has commented incisively: "Every scientist feels acutely today the effects of overspecialization. The volume of publication is so vast that it is impossible to keep abreast of it, even as the field of interest is narrowed. Whole new sciences and branches of engineering appear, with their specialized societies and journals. Intensely progressive gatherings of research workers develop their own jargons, unintelligible except to the initiated, heightening the barriers which separate their work from the main stream of progress."*

How aptly these remarks apply, for example, to the field of cardiovascular diseases is at once apparent to those who struggle to maintain a working acquaintance with current activities dealing with the circulation. The mass of material to be sifted induces a feeling of hopelessness, for much of it is good and merits attention. Even though the basic causes of rheumatic fever, hypertension and atherosclerosis remain obscure, the twentieth century has witnessed giant forward strides. One instance is freshly in mind. In 1929 a young German surgeon, Forssmann, first introduced a catheter into the heart through an arm vein, using himself as the subject. Subsequently, in this city, Cournand and Richards demonstrated how cardiac catheterization could be employed to unravel the intricacies of cardiopulmonary physiology, both normal and pathologic. Last month these three pioneers shared the Nobel Prize in Medicine. The results of their work have made it possible to define more clearly the indications for treatment, medical as well as surgical, of various disorders of the heart and lungs. Such fruitful studies afford a potent stimulus to further effort.

The Academy sponsors a number of specialties which are represented by its twelve sections and by various independent organizations, such as The New York Heart Association. Section meetings are often

* Bush, V. Science in medicine and related fields. *Med. Ann. District of Columbia. 22*:1-6; 58, 1953.

combined and, at the Stated Meetings and under the auspices of the endowed lectureships, an attempt is made to integrate different medical interests. The same concept is followed in arranging the Graduate Fortnight. Because there are many clinics and conferences held at the medical schools and hospitals of the city, which offer postgraduate instruction of a high order, the attendance at some of the Academy sessions has been discouragingly small. Less frequent gatherings, more authoritative speakers and well-chosen topics are lures which attract an eager audience. Lively and informal discussion adds zest to the occasion; random questions from the floor, sent to the platform on torn scraps of paper, rarely evoke a profitable response. In short, there must be fostered an atmosphere of genuine intellectual interest spiced with a practical flavor.

The objects of this association are clearly stated in Article I of the Constitution, a document which only recently has occupied my attention and which, I venture to assume, has not been read by most of you. These are "the advancement of the science and art of medicine, the maintenance of a public medical library and the promotion of public health and medical education." It is the responsibility and duty of all of us to strive for the accomplishment of these purposes.

TWO YEARS OF THE PRESIDENCY OF THE NEW YORK ACADEMY OF MEDICINE*

Address of the Retiring President

EDWARD J. DONOVAN

In the past, it has been the custom for the retiring President in his farewell address, to give an account of his stewardship by reading a long, drawn-out report of each department of the Academy. As this is not only very hard to read, but equally hard for the audience to listen to, I am departing from the custom, and I am sure the same result can be obtained by stating that The New York Academy of Medicine is enjoying most vigorous good health in every department. My plan, then, for this, my final address, is to report on several of the many interesting events which have occurred at the Academy during my two years as President, i.e., events which have made a lasting impression upon me.

The Academy, as you know, receives numerous requests for the solution of difficult medical problems. Many of these requests come from municipal or state agencies but they often come from some remote part of the United States. I wish to report very briefly upon four problems, solved here recently, which may give you some insight into one of the Academy's most important functions.

Perinatal Mortality—Report I. The first of these reports dealt with perinatal mortality in New York City and represented the culmination of five years' study of neonatal mortality by our Committee on Public Health. In this study, the deaths of approximately one thousand newborn infants were thoroughly investigated. Analysis of the records indicated that in one-third of the number, shortcomings were found in the care given either by the physician, the hospital or the family. The

* Delivered at the Annual Meeting of The New York Academy of Medicine, January 3, 1957.

factors listed as responsible for the deaths were: unavoidable disaster, faulty prenatal care, errors in medical judgment, errors in medical technique, family inadequacies, unsatisfactory pediatric care, and intercurrent infection. The great importance of these findings for the current situation in New York City is strikingly brought out by the perinatal mortality rates for 1954-1955. By Health Department convention, the perinatal period extends from twenty-eight weeks' gestation to seven days after birth. During 1955, 5,154 deaths occurred during this period. The rate for 1955 increased six per cent over that for 1954, due almost wholly to an increase in neonatal deaths. Ninety per cent of the deaths in the neonatal period, which extends through the first 27 days of life, occurred in the first week.

In the light of these figures, the significance of this valuable study of the Committee is obvious. By revealing the circumstances contributing to the deaths of infants during the perinatal period, it becomes possible to institute measures to obviate them and reduce the perinatal mortality rate in New York City. On the basis of the Committee's findings the New York City Department of Health has inaugurated a five-point program, designed to lower perinatal mortality.

Use of Barbiturates—Report II. Because of reports on increased misuse of barbiturates, the Committee on Public Health considered the problem of barbiturates in all of its ramifications. It brought together data on barbiturate poisonings both fatal and non-fatal, in England, Wales, the United States, and New York City. It was found that the rate in New York City for 1954 was more than twice that of 1945. In 1954 it reached a peak of 123.3 per million living persons. It became clear that the incidence of both fatal and non-fatal barbiturate poisoning is of such a magnitude that it constitutes a problem in public health.

The report also called attention to the fact that there exists all too much unrest, tension and anxiety in the public. In a fundamental approach to a solution, what is needed is a study of the causes of this unrest and anxiety.

As rational steps towards stopping the misuse of barbiturates and reducing the present high rate of incidence of barbiturate poisoning, the Committee offered four recommendations:

1. The model law controlling the manufacture and distribution of barbiturates should be adopted by all the states. Large cities with

"home rule" should also have laws patterned after this act.

2. A realistic effort toward enforcement of the model law, when enacted, is an essential step. An adequate staff of inspectors to examine records should be organized. Efforts at enforcement should be concentrated on the large cities, where the rates of barbiturate poisoning are the highest.

3. An educational campaign should be conducted by health departments and medical and pharmaceutical societies to remind their members of their responsibility to acquaint patients with the dangers of misuse of barbiturates. At the same time there should be a campaign, using all media, to inform the public of the risks attached to the misuse of barbiturates.

4. Above all, it is highly desirable that adequate funds should be provided to support research on the causes of unrest, anxiety and tension that are so prevalent among the population and are the basis for such great use and misuse of barbiturates.

Impartial Medical Testimony—Report III. Another outstanding achievement of the year was the publication by the Macmillan Company of the report on the Medical Expert Testimony Project. This experiment, which provided expert medical panels as consultants to the Supreme Court judges in cases where conflicting or confusing medical testimony occurred, was sponsored by the Association of the Bar, The New York Academy of Medicine, the Medical Society of the County of New York, and the New York County Lawyers Association. The experimental project, covering a period of two years, was so eminently successful from the standpoints of better medical testimony, more equitable judgments and accelerated settlements of personal liability and injury cases, that the procedure evolved has been incorporated into the regular judicial machinery and budget of our local Supreme Court, without supplementation of funds from outside sources, which, in the first instance, were provided by the Alfred P. Sloan Foundation and the Ford Motor Company Fund. The report has received most favorable comment in both medical and law reviews. The plan has been adopted and put into operation by other communities, notably in Baltimore and in some of the western cities.

Narcotic Addiction—Report IV. After a comprehensive study, the Committee on Public Health published a report on drug addiction and

pointed out that drug addiction has its social and economic as well as its medical aspects. Its promotion is big business which aims to expand its market with fantastically high profits. The more active the Narcotics Bureau, the greater the risk to the ring, the higher the price of the product and the greater the financial profit. Addiction is more alarming and tragic than ever, because it is believed that a large proportion of the new recruits are adolescents. Drug addiction is an exceedingly expensive habit. Driven by his irresistible craving for the drug, the addict is compelled to become a peddler or "pusher" of it in order to obtain it for his personal use. In this vicious circle of events, he attempts to build up a list of new customers. By leading them into a life of narcotic servitude, he contributes to the spread of addiction.

It is easier and more effective to prevent drug addiction than to cure it. The sensible objective is to stop the flow of new recruits. In time, drug addiction might be reduced to a minimum and perhaps disappear. All on the side of law and order agree on the objective but differ sharply over the means. Until recently, the prevailing attitude has been that all engaged in the illicit drug market, including the "pushers" who are usually addicts, are criminals and should be subject to strong punitive action. This attitude makes the addict distrustful of society and discourages him from revealing his habit and seeking treatment. It is one reason why the proportion of addicts receiving treatment has never been great. Recently, segments of the medical profession and the bar have expressed the view that drug addiction falls within the province of psychological disturbances. It is their opinion that an addict is a sick person, not a criminal. Hence, he should be treated, not punished. It should be emphasized that the non-addict trafficker is not included in this category.

In its report on drug addiction, the Committee drew a series of conclusions on the existing situation. It pointed out that the crux of the objective to stamp out drug addiction is to diminish the number of individuals becoming newly addicted. As a second objective, efforts should be directed to rehabilitate as many presently addicted persons as possible. Such efforts could not only reduce the prevalence, but contribute to stopping the increase of addiction. The Committee proposed a six point program to achieve these objectives. It urged that all six measures should be instituted.

1. There should be a change in attitude toward the addict; he is a

sick person, not a criminal.

2. The most effective way to eradicate drug addiction is to take the profit out of the illicit drug traffic.

3. An integral part of the program would be medical supervision of existing addicts with vigorous efforts aimed at their rehabilitation.

4. There should be no relaxation of efforts toward complete and permanent elimination of the supply of illegal narcotic drugs and provisions for suppression of the illegal traffic should be retained. But the law should draw a distinction between the addict and non-addict in its provisions. The convicted non-addict trafficker should feel the law's full force.

5. There should be a vigorous educational program directed toward the general public on the dangers of narcotic drugs.

6. The magnitude and pathogenesis of drug addiction should be studied. It is a merit of the medical approach that by adopting the proper attitude toward addicts, it would be possible to obtain answers to these questions.

It is the opinion of the Committee that this program, taken in its entirety, is a reasonable and humane approach to the solution of drug addiction. It must be frankly admitted that there is no ideal or perfect solution. Of the two possible approaches to the solution of the problem, the punitive as against the medical, it becomes a matter of judgment as to which gives the more promise of effectiveness, and contains fewer points of vulnerability. In judging between them, the Committee believes that the evidence is preponderantly in favor of its proposed program as the more promising means of ridding the nation of drug addiction.

One of the many things about the Academy that has impressed me most favorably is the improvement in and the high standard set by the Academy Bulletin which is the chief means of expression to the medical public of the Academy's activities. While the Bulletin has always been something of which the Academy was justly proud, it has improved in so many ways in recent years, including increased circulation, that the Academy can take great pride in its accomplishments. This change is due, in part, to the diligent efforts of the Editor and to the members of the Bulletin Editorial Board, who have been most careful in the selection of material for publication. The Bulletin has now become one of the foremost of the current medical journals.

Like all institutions of its kind, the Academy has suffered somewhat from a decrease in the attendance at its medical meetings, despite the high quality of the programs presented. Until a few years ago, practically all medical meetings in New York were held at the Academy, but now the medical colleges, the various hospitals and numerous special medical societies, all have their own meetings, at which almost compulsory attendance on the part of their members and staffs is required in order for the institutions to maintain their accreditation. The point has now been reached where there are just too many medical meetings and the complaint on all sides is that if one were to attend all of these meetings he would have no time whatever for his family. There is no doubt that this is a problem of great importance, with many contributing causes. The Academy feels that this is the type of problem which should be studied here, and in thinking seriously of its solution, we have been led to the belief that the first step was probably the need for a complete survey of the Academy, to determine first if our position as a postgraduate teaching institution has changed with the changing times. Should we have fewer Academy meetings, should some of the meetings of the sections, which for years have presented many monthly programs, be reduced in number? Numerous possible causes for the decreasing attendance have been suggested, such as a need for better parking facilities at the Academy. Many members still believe that the lack of available parking facilities keeps many from attending meetings. We realize that the decreased attendance is not confined to New York nor to medical meetings alone, as it is a universal problem throughout the United States as well as in many foreign cities and in numerous fields of endeavor.

In order to study these many problems which affect the Academy, a rather large committee will be appointed early in the new year to survey the activities of the Academy and their manifold ramifications. I have appointed Dr. Wm. Barclay Parsons to be chairman of this Committee which will not be expected to submit its report and recommendations for several months. It is my hope that under your new President, this Committee will give fresh direction and orientation to the Academy and its activities. To produce the result we desire, will call for full cooperation on the part of everyone concerned, and I feel confident that this cooperation will be forthcoming. We are all hoping that this survey may bring forth the solution of many of the

problems with which the Academy is concerned and determine particularly what our place in postgraduate medical education is.

It might be well at this point to speak briefly about our efforts to solve our parking problem at the Academy. Almost everyone has a parking problem today, but since our situation has been given so frequently as the cause of decreased attendance at meetings, it seemed worth while to investigate further. With the demolition of three tenements adjacent to the Academy on 103rd Street, we obtained a vacant lot 100 x 75 feet which we thought might be used for parking. We consulted a group of parking experts who, after considerable study, stated that we had three choices. 1) Fence and pave the property and make a simple parking lot which would cost very little. But since this area could accommodate only 24 cars, it would in no way solve our problem. 2) Build a ramp garage which would provide space for two or three times as many cars but which would be expensive to erect and to maintain, as it would need two attendants at a salary of $4500 each per year. 3) We could build what is called a pigeon hole garage, several stories high, entirely automatic, which would accommodate many more cars but might cost $200,000. The experts finally advised us to give up the idea of establishing parking facilities on a large scale at the Academy, as it would be so costly as to be impractical. However, we have decided to make the space into an attended parking lot of the simplest type available free of charge to Fellows of the Academy from the hours of 4:00 p.m. to midnight, the hours when they need it most. This will accommodate all of the cars now parked on both sides of 103rd Street between Fifth and Madison Avenues, and will at least supply a rough estimate of the actual demand for parking space.

Several structural changes in the Academy building have been made in the past year. Most notable of these was the complete renovation of the Presidents' Gallery and the Reception Room directly adjacent to it. Complete wood panelling of the Gallery walls and the installation of new ventilating and lighting systems have added greatly to the comfort of these rooms. The Presidents' Gallery has been made more attractive by displaying many portraits of recent Presidents.

There are many important lectures and conferences held annually at the Academy some of which I would like to mention briefly. 1) One of the most attractive of these is the Health Education Conference

attended by Health Educators from all of the Eastern States and from parts of Canada. Two days each year are devoted to this meeting which provides an opportunity to hear from the most distinguished health educators in the country. 2) A group of Lectures to the Laity on medical subjects, is another of the most outstanding series. This annual lecture series was originated 22 years ago and in recent years the lectures have been broadcast over Radio Station WNYC. They have been very popular. 3) The observance of the Freud Centenary held on April 20th of the past year, was very successful. Some of the most notable psychiatrists and psychoanalysts in the country spoke on various aspects of Freud's life and activities, to one of the largest audiences at the Academy this year. 4) The Graduate Fortnight has been held annually since 1928 and continues to attract great interest in medical lectures at the postgraduate level. 5) The FM lectures have continued to be broadcast over Radio Station WNYC on each Thursday evening as for the past several years.

To our regret Miss Janet Doe retired this year as Head Librarian of the Academy. Miss Doe joined our Library staff in 1926, became Assistant Librarian in 1930 and was appointed Head Librarian in 1949. She has given 30 years of diligent, efficient and devoted service to the Academy and in her leaving, the Academy sustains a great loss. She is without question one of the most distinguished medical librarians in this country and as the result of her diligence, our medical library is today one of the two largest in North and South America and our greatest asset. We shall always owe Miss Doe a great debt of gratitude. We are fortunate, however, that Miss Doe's associate, Miss Gertrude Annan, was appointed Head Librarian, which made our loss easier to bear.

The healthy state of the Academy mentioned earlier, of course implies that the Academy finances are in excellent condition and this is due in large measure to our very efficient Board of Trustees. For 1956, the Academy budget amounted to $617,802. You may wish to know the source of these funds. Yield on investments produces the largest share, the balance coming from dues, proceeds from the Bulletin, contributions, library fees, etc.

My two year term as President of the Academy of Medicine comes to a close this evening. It has been a delightful experience and a most valuable postgraduate medical education for me. One of the most

pleasant parts of this experience is getting to know well, a large segment of the Fellowship of the Academy who, without question, represent the best in medical practice in New York. Our Board of Trustees has been most cooperative and helpful to me, as have all of the Executive Secretaries of the various committees and their assistants. Words cannot express my admiration for nor my gratitude to, our very able Director, Dr. Howard Reid Craig, whose advice and support have been most helpful to me on numerous occasions during the past two years. In fact, there is no one at the Academy who has not made a real effort to make my term as President most pleasant. I wish now to extend to everyone in any way connected with the Academy of Medicine, my heartfelt thanks.

I am very happy that our new President is Dr. Robert L. Levy, who has served two years as Vice President of the Academy and who at all times has had the Academy's welfare at heart. I am confident that he will be most successful as our President and I extend to him my very best wishes.

THE PRIESTHOOD OF MEDICINE*

Anniversary Discourse

CHARLES GARSIDE, LL.D.

Chairman of the Board and President, Associated Hospital Service of New York

MR. PRESIDENT and Fellows of the Academy:

I deem it a signal honor to be asked to deliver the Anniversary Discourse this year. The maturity of your collective judgment is reflected in the nomenclature you employ. You do not attempt to dignify it by calling this an "address" or "speech". You call it what it should be called—a discourse. A few minutes of after-dinner discourse is about all that a prudent man dares to offer, and about all that a body of cultivated men can take.

It might be helpful if I adhere to the tradition of integrity which characterizes the Academy, and state in the beginning that I have nothing new to tell you. "The minds of men do not throw up sudden stray ideas without ancestors and precedents. History is perfect continuity. There is no spontaneous generation." I wish those were my words but they are not. They are from an essay treating of the history of ideas by Ortega, the great Spanish philosopher. These words came forcibly to my mind a year or more ago when I was honored by a visit from a distinguished member of the Australian senate. For reasons based on faulty communications he sought me out, rather than someone better qualified, to see and learn something of our great medical centers. We spent an afternoon inspecting the awesome equipment of one of our magnificent hospitals. He was amazed at what he saw and learned. But when we sat together later, as two laymen, for a sadly superficial discussion of modern medicine, he remarked, "You know my grandmother migrated to Australia from Ireland. She always used to keep a supply of well molded cheese on hand which was used for wounds, cuts and surface infections, which were common in those days of pioneering. She said that her parents in Ireland had done the same.

* Presented at the Annual Meeting of The New York Academy of Medicine, January 3, 1957.

She was probably using a kind of penicillin, but didn't know it."

There will be nothing new in what I say but it will represent a point of view which I believe should be emphasized. This body constitutes a corps d'elite of medicine. You are the custodian of its great history and its lofty ideals. If these ideals fall far short of realization by the profession as a whole, you must not be discouraged or impatient. Like St. Paul you must strive for better things than you are able to attain. But here in the Academy you can be seen trying to achieve your ideals.

The ancient Hippocratic Oath, some form of which you all solemnly swore to when you entered upon the practice of medicine, contains a beautiful sentence of great significance. As I shall later endeavor to emphasize, it becomes increasingly significant today. It reads "With purity and holiness will I pass my life and practice my art." Why was this pledge incorporated in the original Oath? Because you cannot be true to the other and more specific pledges in the Oath, and not live a life of purity and holiness. You cannot preserve unsullied the relationship between doctor and patient called for in the Hippocratic Oath without embracing the Priesthood of Medicine. It was so twenty-four centuries ago; it is so today. Only a layman who has enjoyed the blessing of the relationship can fully comprehend this.

The doctor does not ignore it or forget it but he is so absorbed in his life work, particularly in the scientific and technical side of it, that he often does not see it in perspective. It is a simple truism that doctors are told more of the secrets in men's hearts than are the clergy. To be sure, a man will confess his sins to a priest, but to his doctor he tells all that affects mind, body or soul, be it sin or no. Standing in such a relationship to his fellow men, how can a good doctor be other than pure and holy in the sight of God?

There may well be some questions today concerning exactly what is meant by the words purity and holiness, but we can all agree that they certainly mean goodness, if not saintliness.

Through the centuries, in dark ages and in brighter ages, through plague, storm and distress, the doctor has ministered to the needs of man. In our complex society some corporate and cooperative methods are required by the profession, but the priesthood must remain. While doctors must work together for the general welfare, they will still be working as individuals for individuals—as persons for persons—as living men for living men.

Notwithstanding the passage of time and the complexities of modern society, we must return to the Greeks and to Hippocrates for the beginning of this concept of the doctor-patient relationship. Because of their respect for the dead, they were permitted to examine only living men and women. Not only were they concerned with the life of man; they were concerned with his relationship to the world in which he lived. We find in Plato a significant reference to this concern. In the Phaedrus, Socrates asked: "Do you think it possible then, satisfactorily to comprehend the nature of soul apart from the nature of the universe?" To which question Phaedrus answers: "Nay, if we are to believe Hippocrates, of the Asclepiad family, we cannot learn even about the body unless we follow this method of procedure." And Socrates replies: "Yes, my friend, and he is right."

Let us simplify this a bit and think, not in terms of the universe, which is difficult of comprehension for any man, but let us call it the nature of the community and man's relation to it. While the Greeks thought in terms of man's relation to the universe, the business of modern living consists largely of man's groping for adjustment with his fellow men and with the community of which he is a part. His ailments, physical, mental and spiritual, are all involved in this groping. Is it any wonder then that modern medicine puts new emphasis on the doctor-patient relationship, the nature of personality, man's relation to his fellow men and the significance of psychoneurotic behavior. While we move forward, we retrace our steps back to Hippocrates. The techniques of medicine have changed century after century, year after year, but the principles of the profession have not changed. The Priesthood of Medicine remains. In truth it would seem that, in a broad sense, we are returning to that curious admixture of medicine and philosophy which characterized the Corpus Hippocraticum. In consequence, the doctors of today and tomorrow must know more about more things than any other body of men.

We may need more doctors, and we may need a better distribution of doctors. We may have to evolve some new methods to support our expensive medical schools. We may need further changes in the curricula of medical schools. (The body of medical knowledge is already so extensive that about all a good medical school can accomplish is to teach a man or woman to think as a doctor.) It is probably true that doctors should play a larger role as citizens in our democracy. It is

pretty clear that we must continue to search for methods to bring our fine medical care to more people. But if all or any of these ends be desirable and they are attained, it will avail us nothing if we deviate from the fundamental nature of the doctor-patient relationship. Unless there be a Priesthood of Medicine holding high the torch that has been carried for twenty-four centuries, no ultimate good can come from the realization of any of these ends.

Why do I emphasize this doctor-patient relationship? Why do I emphasize the art rather than the technique of the profession? It is because I have for ten years talked of the overemphasis on scientific and technical training with consequent neglect of the humanities. Over and over again I have stated that there is an imbalance between scientific training and the humanities. We are producing more and more trained men and fewer and fewer educated men. All of our twentieth century failures have been in the field of human relations. We seem to know a lot about molecules but little about men. Progress in science may be deemed essential to our preservation but what will there be left to preserve if we continue to commit blunders that grow out of our failure to understand human values and the vagaries of human conduct?

If in your mind's eye you see the first half of this century in panorama, there is little to give you solid comfort. We have produced an Einstein, a Ford, two catastrophic wars, many lesser wars, and the atom bomb. We have had no Emerson, Thoreau, Whitman or Lincoln. We have lived through a life span of scientific achievement and we have produced in that time not a single new thought about the nature of man and what he is here for. Through your profession we have extended the life expectancy of human beings but what have we done to provide them with happier lives? Of course we must teach science and pursue scientific research but we do not have to worship science as a graven image and neglect the study of man in so doing!

It is here that the doctor of medicine enters the picture. He has a solid basic scientific training but his problem is still man. Contemplate how little a doctor knew of curing sickness a half century ago, and yet he was revered as a saint and even as a prophet. His advice was sought by all members of the community. In recent years the doctor has been so preoccupied with the scientific side of his profession that he has tended to neglect human relations. He has not made the contribution he should make toward the solution of human problems. Even the

present generation of doctors, probably overburdened with scientific knowledge, is better equipped to teach us the nature of man than is any other profession. No man is in position to contribute so much to improvement in human relations as is the doctor.

As we make further progress in improving the curricula of our medical schools, the doctor's contribution can be far greater. You all know members of the profession today who regret that they had so little of the humanities in college before entering medical school. They saturated themselves with the basic sciences and neglected art, music, literature and history. As we move forward in the direction of what Dean Berry calls "comprehensive medicine" (and I am sure Dean Rappleye will use the same phrase), the doctor should be prepared to play a larger role in the life of the community. What the community obviously needs is greater wisdom in dealing with its problems. The cultivated doctor of medicine by the very nature of his life work acquires wisdom. He learns what it is that makes man tick. His advice should be invaluable in all the problems that involve man's relation to man. You will recall that your great colleague, Alan Gregg, once remarked that "There are no diseases, there are only sick people." My point is that, without neglecting disease, you bear down on people and help all of us to solve the complex problem of living in this second half of the twentieth century.

When I studied philosophy in college, I read Liebnitz. Liebnitz was a believer in atomism but he wanted to be an idealist. He therefore worked out an atomism that was, at least so he thought, free from the materialism which traditionally characterized it. He observed that a point is not a line but that a line is made up of points. In other words, a thing may be made up of parts that are different from the whole. If you make a line smaller and smaller you get a point, and yet a point is not a line. Therefore you get something you did not have to start with. Reasoning thus, he held that if you reduce matter, and reduce it, you reach a point where you no longer have matter. There is still something left, however, and this something Liebnitz called monad or spirit.

Thus it is when one is preoccupied with science. When you get all through reducing everything to a mathematical equation there is something left which cannot be explained away. There is something which a human being craves. This may be the reason why the scientific age has produced a sense of insecurity which is probably the most char-

pretty clear that we must continue to search for methods to bring our fine medical care to more people. But if all or any of these ends be desirable and they are attained, it will avail us nothing if we deviate from the fundamental nature of the doctor-patient relationship. Unless there be a Priesthood of Medicine holding high the torch that has been carried for twenty-four centuries, no ultimate good can come from the realization of any of these ends.

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Thus it is when one is preoccupied with science. When you get all through reducing everything to a mathematical equation there is something left which cannot be explained away. There is something which a human being craves. This may be the reason why the scientific age has produced a sense of insecurity which is probably the most char-

acteristic thing about it. The human being craves something from his doctor besides technical knowledge. Of course he wants to be cured of sickness, but he wants affection, warmth and understanding.

If man cannot live by mathematical equations, it certainly follows that he cannot adjust the complex group relationships of our modern society by mathematical formulae. The scientist loves to see the equation solved. He likes things to come out just right—with no messy details left over to plague him. Well, when you are dealing with men, you will find that men simply do not parse. You are up against human whim and caprice. Here we enter the field of the social scientist. Social science is sometimes referred to as the newest discipline—the offspring of a pretended marriage between science and humanities. This is not true, because the first social scientist lived back in the dark ages, and was the man who worked out some simple rules whereby the family, and later the tribe, could live together without daily violence and murder. Social science is a new discipline only in the sense that not until recent years has its significance to society been appreciated, and its serious students been given appropriate recognition.

The truth is that in the settlement of this vast country of ours, from our beginnings in the east to our development of the west the doctor was a conspicuous social scientist. He had much to do with adjusting differences, advising settlers and keeping peace in the community. The doctor of that generation carried a little black bag containing a few pills. His medical education was pathetic but he was likely to have read the Bible, Shakespeare, Milton and Burns. He may also have studied Greek, Latin and Hebrew. He began where one must always begin—with the humanities. You must know something about man and the history of man, for it is man you work with.

And now, what little knowledge of human relations I have tells me that I have talked long enough. I have enjoyed this Discourse. It has been fun to think out loud with you. I have endeavored to emphasize the art of your profession. I have urged that you do not neglect man, as you continue to make remarkable strides in science. I would also dare to suggest that the profession be not overly preoccupied with what is unhappily called medical economics. I have often wished that more felicitous words could be found to describe the essential work which doctors do in this field. I would also suggest that the profession avoid controversies with hospitals. Here in New York we have been particu-

larly fortunate in this respect, and I believe the high standards of the Academy have had much to do with this agreeable fact. And of course avoid controversies with governmental bodies so far as possible. All of these suggestions embrace the broad field of human relations.

I would suggest that you continue here in the Academy to set a very high standard of conduct—even if you know that the entire body of medicine will not always adhere to it. I urge that you use to the full your enormous opportunities for contributing to the general welfare. I urge that you preserve unsullied the great traditions of the profession—traditions that may be traced back over two thousand years; from Hippocrates to Galen; from the Alexandrian School to the Arabic School; then the Schola Salernitana of the early Middle Ages (the same Salerno not far from which some of you practiced your profession under battle conditions but a few years ago); then Jewish scholars working by candle light under Catholic Bishops, translating the medical learning of the ancients; then the School of Montpellier; then Padua, and down through the more recent centuries we trace the continuity of your great traditions. Here we have the same continuity of history to which I earlier made reference. Often there was little of scientific knowledge but always there was the art of the profession. Throughout the years the thing that has always mattered was man—man and his need for help in his sickness. And throughout the years the Priesthood of Medicine has cared for and comforted man. May it always be so.

A CLINICAL EVALUATION OF ANTIHYPERTENSIVE DRUGS*

IRVINE H. PAGE

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THE past ten years have seen the transition from an era of almost drugless therapy of arterial hypertension to one which baffles the clinician with its multiplicity of drugs. It is good now and again to stop amid the claims and counterclaims and take stock of what has been accomplished and what needs doing. Maybe there are so many drugs now available because, like women's hats, no one likes to make the same mistake twice.

GOALS OF ANTIHYPERTENSIVE DRUG THERAPY

First let us look at what we are trying to do. As I see it, we want 1) to reduce arterial pressure to as near normal levels as possible except in advanced arteriosclerotic hypertension; 2) to induce few side effects; 3) to prevent the cardiovascular disease which usually accompanies hypertension; 4) to prolong life and to make it more pleasant and comfortable; 5) to keep expenses reasonable.

How far along are we in our search for these desirable objectives? I should think not very far, yet the first vital step has been taken and investigators and clinicians alike are alert to the need of antihypertensive drug therapy. The old Cohnheim conception that blood pressure is elevated to insure adequate perfusion of tissues seems to have died a quiet death, which is just as well. At last the drug manufacturers are also working hard on the problem and now constitute the chief source—usually the only source—of experimental drugs. It is puzzling that manufacturers were so slow in taking up the problem, but now, once under way, their program is proving quite effective. Much the same turn of events is now occurring in the fields of atherosclerosis and neurochemistry.

* Presented at the 29th Annual Graduate Fortnight of The New York Academy of Medicine, October 17, 1956.

Can arterial pressure be reduced satisfyingly by the drugs now available? I estimate that this is possible in about half the patients. The other half is anything but satisfying. There usually are temporary falls in arterial pressure with each new drug used but the falls do not last and another drug is tried with much the same lack of success. This fact proves beyond doubt that we are far from our goal of adequate blood pressure reduction.

Side effects are so common with all of the drugs now available that they are almost taken for granted. One has only to think of the parasympathetic effects of ganglion blocking agents to realize how much we have had to accept as the price for lowering blood pressure.

We have pointed out[1] after 26 years of trying to treat hypertension, that, while ability to lower blood pressure has improved, the prevention and treatment of the accompanying cardiovascular disease has advanced little. It is true that most evidence now strongly suggests that heart and blood vessel disease is less likely to occur when blood pressure is held within normal limits; consequently, what progress has been made has been the result of keeping the blood pressure down. The contrary view that the vascular disease precedes the hypertension has received little support recently. But until we know more about the treatment of the vascular disease and especially that in the cerebral, cardiac and renal areas, the problem of treatment of arterial hypertension will not have been solved. It is a complicated and difficult one but its pervading importance must nudge us into greater effort.

Whether, as physicians, we have made life richer and more comfortable as a result of drug therapy is a problem I approach with some misgivings. I am certain that we have all made some patients miserable. But, on balance, I would guess that the net effort has been for the better. Without being able to prove it, I believe that many patients' lives have been usefully prolonged. Of one thing I am certain, and that is that the vascular changes of malignant hypertension can be reversed, a phenomenon I saw for the first time following anterior spinal nerve root section. For those of you who are young, this was the operation devised by Adson which preceded the more modern sympathetic ganglionectomy such as that of Smithwick.

Currently we are in a highly experimental phase in the use of antihypertensive drugs. All sorts of chemicals are under test in the hope that they will prove useful. This does not make it easy for our

patients but I see no way, after animal tests are completed, of avoiding the crucial test on the hypertensive patient.

It is the side effects of the antihypertensive drugs in most cases which cause the discomfort. These miseries are no strangers to you, a group of practicing physicians, and I will not insult your experience by recounting them. I would like to point out that there is a growing list of syndromes, some of them fascinating, which are iatrogenic, but which when their mechanisms are understood, will give important understanding of disease of the most varied nature. I refer, for example, to hydralazine disease, which elicits both a rheumatoid arthritis-like state and a lupus erythematosus-like one.

To some degree comfort and expense go hand in hand. Hypertension is a chronic state often lasting several decades. For this reason alone, the cost of the drugs prescribed should receive consideration. Some will say this is not the province of the physician. I disagree. Finance is one of the important stresses and strains to which the hypertensive is subjected. It is often at the very heart of the mechanisms of hypertension. Every effort must be made by manufacturers to price their products reasonably, to reduce advertising costs to a minimum and provide as much stability in the market as is consistent with advance in knowledge. As more and more chronic diseases such as hypertension and arteriosclerosis are being added to the list of those possibly amenable to drug therapy, the financial problem becomes progressively more urgent.

Difficulties of Objective Evaluation of Drug Action

One fact always puzzles the newcomer in the field of hypertension. How can there be such a variety of results and interpretations when a given drug is used in the same type of patients by different investigators? Let's be very personal and take examples from the current literature written by competent observers about the same drug, reserpine. Bello and Turner[2] find ". . . the drug had no significant effect on pulse or blood pressure." But listen to Smith and his associates.[3] "Sixty-three percent of the patients had become normotensive by the conclusion of the study." Appearing in the same journal and within a short time of each other, the reader must be left wondering. The same type of illustration is found in the problem of toxicity with some observers finding none and others describing the most alarming reactions. This

confusion is not limited to the Rauwolfia drugs. As nearly as I can discern, the English clinicians in general think very poorly of hydralazine (Apresoline) while in this country, Germany, Denmark and Sweden, it seems to have become established as a useful drug once its idiosyncrasies were understood. It is an almost black and white contrast.

I don't want to belabor the point because I think most clinicians are aware of both the confusion in the literature and how badly it is in need of having the white of an egg dropped into it. I shall be content to stress only three more points.

1. The therapeutic effectiveness of a drug appears to depend on its ability to lower arterial pressure sufficiently to prevent the progress of vascular disease and relieve the load on the heart. One often reads that such and such a drug lowers blood pressure "significantly" but the reader is not informed what the author considers "significant" from a practical clinical point of view. I mean by "significant" what I have just said. Even the question of the validity of a cause and effect relationship between treatment given and the effect on blood pressure periodically comes under fire. A particularly devastating examination of the problem has recently been published by Goldring, Chasis, Schreiner and Smith.[4] Intensive reassurance with the aid of an "atom gun" brou[illegible] an average decrease of 38/28 mm. Hg which is considerably better than some of the "significant" falls recorded for some drugs. But even this type of study depends much on the kind of controls that were used.

2. The second point is one that always seems to arouse my diencephalic centers with perhaps some associated cortical inhibition. It is the view that arterial hypertension is a unitary disease. I am sure most realize this is not true, but often they don't act as though they do. Why would it be expected that a drug which acts primarily on one mechanism, would reduce pressure with any degree of specificity if an entirely different mechanism were involved. If, for example, the nervous system were blocked off by hexamethonium, moderate fall in blood pressure would occur even if the nervous system were just doing its normal task and not involved in the mechanism of the hypertension. If the hypertension were being maintained by some renal factor, the loss of nervous tone would not be expected to abolish it.

3. There seems to be a growing tendency to believe that the larger the series the greater the accuracy of the results. Instead of studying 10 or 50 cases thoroughly, hundreds or thousands now seem

to be necessary to carry conviction. I am baffled by the casual bandying of the 300 to 3000 patients who were studied personally by one man. The simplest reflection shows that such a study could only be superficial in the extreme; a few scattered blood pressure readings in an office, often spaced months or years apart, administration of a drug and more scattered pressure measurements. These data become a figure in a printed column spelling success or failure of treatment. I submit that this sort of study may be worse than useless because it can so often be misleading. I remember one day trying to flatter your and my old and respected friend, Dr. Alfred Cohn, while we were seeing a patient with coarctation of the aorta. I said I knew from the many cases he had seen that this one had nothing new for him. He replied that he had seen innumerable patients with coarctation but had studied two. Like Dr. Cohn, I find myself singularly unimpressed by "bulk method" of studying hypertensives.

These are only some of the facts illustrating why there is not more unanimity about the value of particular drugs in the treatment of arterial hypertension. Until we know more about the specific mechanisms involved, it is unlikely the situation will improve very much. There are few fields in which so many leads have been opened for investigation and so few of them being followed up. Despite the great demand for, and sale of, antihypertensive drugs, fundamental research on the nature of hypertension is altogether inadequate.

Common Sense and Its Congeners

We are in an era when a pill is often substituted for common sense advice. This is much more apt to be effective in acute than in chronic disease. Patients have to learn to live with themselves and with their disease. The union can be a happy and productive one, depending often upon the pre-marital instruction.

The best initial approach to the patient seems to me to be an educational one; to face the problem of the disease with the patient and to lead him away from fear by teaching him wherein his fear arises. Certainly, infinite patience is required to listen to the initial history of a garrulous woman, what someone has called, "the preamble to her constitution." We use discussion and reading material but I must confess that I don't think we do nearly a good enough job. I have tried to be helpful by writing a manual for hypertension patients which seems,

for reasons entirely unclear to me, to have received more acceptance by physicians than by patients: it has had little impact on the big problem. There is great room for group or class room demonstration and teaching. Rehabilitation, both mental and physical, is a pressing demand with such catastrophes as stroke being such a common cause of morbidity. I wish we did as well in our field as is done by many of the diabetic clinics.

In sum, it would be a pity if we substituted pills for the human warmth and understanding a physician owes his sick patient. The latter are particularly necessary when dealing with chronic diseases. Nor must there be erected too many "don'ts" as road blocks to happiness. Remember, for a good life, be moderate in all things, but don't miss anything. This is my only real "don't."

It is perhaps presumptuous on my part to stress another facet of common sense in the treatment of hypertension. I do it because I hope all of us will be constantly on the alert to better our methods of diagnosis. Little by little small groups of patients with unitary mechanisms are being chipped off of what has appeared to be a monolith. These people often turn out to have correctable defects. I think, for instance, of those we have been uncovering at the Cleveland Clinic where the aortogram has shown defects in the renal vessels correctable by arterial transplants. The urologist and vascular surgeon can make an important therapeutic contribution to this small group of patients.

The time cannot be far off when some creative investigator will find chemical ways of making the correct mechanistic diagnosis and then I am sure that much of the current haze in treatment will be dispelled.

Ganglion Blocking Agents

These substances act by competing for acetylcholine which is the transmitter of nerve impulses passing through autonomic ganglia. While there may be other transmitter substances in ganglia, none are currently recognized.

Except for one, mecamylamine, studied by Freis and Wilson,[5] Moyer and associates[6] and others, all the ganglioplegic agents in current clinical use are quaternary ammonium derivatives. Their chemical structures are similar to that of acetylcholine and they compete with it for receptor sites. Since both sympathetic and parasympathetic ganglia have

the same transmission mechanisms, both become blocked by these agents. I need hardly tell a sophisticated audience like this that herein lies a serious difficulty with these agents.

You are all sufficiently familiar with the actions of these substances not to need me to review them for you. There is still some uncertainty as to the precise physiological mechanisms involved in the lowering of arterial pressure. Probably those[6a] who believe in reduced venous return with reduced cardiac output have somewhat the edge over those[6b, c] who believe more in arteriolar dilatation with reduced peripheral resistance as the prime cause. The two points of view by no means seem to be exclusive and which is the more ascendant may well depend on the state and position of the patient. As an example of what I mean, some patients exhibit clear hypotensive responses when pressure is measured in the supine position; many do not. When those of the latter group stand up their pressures fall sharply and remain lowered. Still others only show a marked hypotensive response when they exercise. Here are the blood pressure measurements of such a patient:

	Supine	Standing	5 minutes walking
Average	210/30	157/109	124/91 mm. Hg

When the patient sat upright on a stationary bicycle and pumped his legs, arterial pressure fell from 142/103 to 122/78 mm. Hg. If, on the contrary, he lay prone and lifted 3 pound weights on each foot blood pressure also fell (194/127 to 162/100). Clearly then, exercise hypotension following ganglioplegics is not necessarily a result of posture, a fact not generally recognized.

The fall in cardiac output with decreased venous return and pooling or trapping of blood theoretically would not be the best way to reduce blood pressure in patients with increased peripheral resistance and normal cardiac output (Crosley and associates[7]). But so far no one has shown that such chronic trapping of blood is harmful. Perhaps fortunately in the kidneys there occurs some decrease in calculated vascular resistance (Del Greco, Corcoran and Page[8]).

With the appearance of each new ganglion blocking agent since hexamethonium, there has been a wave of advertising enthusiasm followed by almost as enthusiastic clinical reports, both of which quietly are forgotten when still another agent appears. In retrospect, it is hard to see that major improvements have been made except for improvement in absorbability. For what they are worth, here are my opinions,

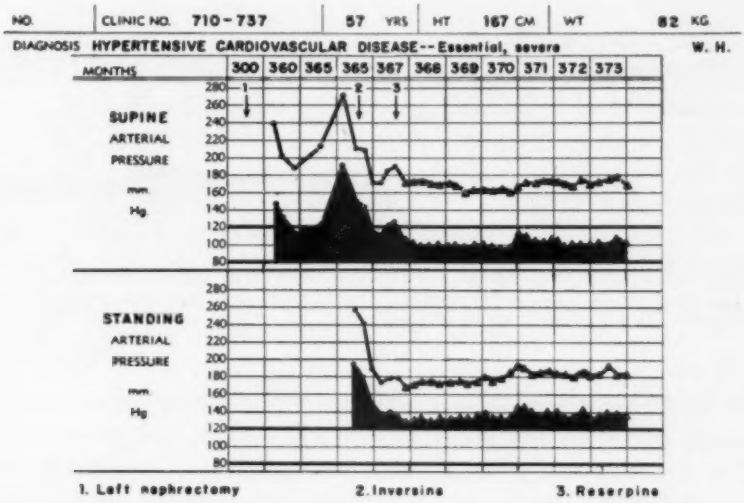

Figure 1.—Example of the effectiveness of mecamylamine in a patient with severe essential hypertension. Each dot on this and succeeding charts represents the average of four daily blood pressures for one week; the vertical divisions separate periods of one month. In this patient the drug elicited lowering in both the supine and standing arterial pressure. The addition of reserpine lowered slightly the dosage of mecamylamine required.

which have to remain opinions until more objective evidence is forthcoming. The absorbability of the drugs has been greatly improved, consequently the danger of irregular absorption seems no longer to exist. The sheer bulk of drug to be swallowed has been reduced. Side effects resulting from parasympathetic blockade are still with us and unabated. Refractoriness appears in some patients with all agents. Whether the length of time of action has been increased is hard to answer; and so far, bear in mind, that no one has presented objective evidence on this point. Our impression is that no great change has been effected. One thing is certain and that is the price has gone up.

Let me summarize briefly our relatively extensive experience with two of the latest substances, mecamylamine (Inversine) and Chlorisondamine (Ecolid). Mecamylamine is unusual in that it is a secondary amine and not a quaternary ammonium compound. It seems to be absorbed completely from the gastrointestinal tract. Schneckloth, Corcoran, Dustan and I[9] found it effective in about one-half of hypertensives given an average dose of 25 mg. It is no more effective in

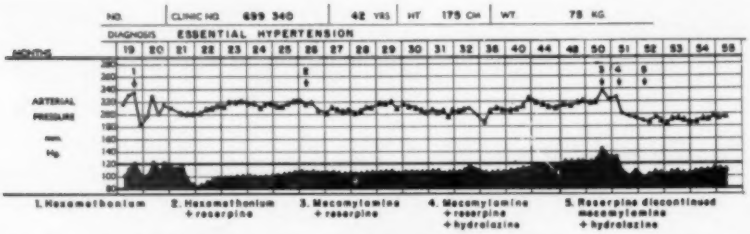
NO.
CLINIC NO. 699 340
42 YRS
HT 175 CM
WT 78 KG
DIAGNOSIS ESSENTIAL HYPERTENSION
MONTHS
19 20 21 22 23 24 25 26 27 28 29 30 31 32 36 40 44 48 50 51 52 53 54 56
ARTERIAL PRESSURE
mm. Hg
1. Hexamethonium
2. Hexamethonium + reserpine
3. Mecamylamine + reserpine
4. Mecamylamine + reserpine + hydralazine
5. Reserpine discontinued mecamylamine + hydralazine

Figure 2.—Gradual loss of response to the ganglion blocking agents hexamethonium and mecamylamine (1-3). Reserpine had little effect (2). Addition of hydralazine again gave a fall in blood pressure (4). Discontinuing reserpine caused no rise in pressure. This illustrates the need for constant supervision of treatment and the search for effectiveness of each drug.

lowering arterial pressure than other ganglion blocking agents and the needed dose from day to day is also variable. This variability can be very disturbing as it is usually entirely unpredictable. Patients are on the whole more sensitive in the morning than in the evening and possibly more so if they are bed-fast. Side effects resulting from parasympathetic paralysis are similar. Constipation often needs to be prevented by diet, cascara or magnesium oxide. At times neostigmine needs to be given to secure a bowel movement. Dryness of the mouth may be combated with 5 to 10 mg. of pilocarpine taken orally about a half hour before meals. The therapeutic advantage lies mainly in the predictability of intestinal absorption and the ease of handling patients on this drug. Contrary to some claims, when refractoriness is induced by other ganglioplegics, response to mecamylamine is also lost in both man and animals.

A neuromuscular disorder has been observed in some of our patients. It manifests itself as anxiety associated with jerky, choreiform movements and tremor, especially of the hands and arms. Bizarre mental aberrations occur and two of our patients had convulsions. Remission occurs on discontinuing the drug. Diffuse hypertensive cerebro- and/or renal vascular damage seems to provide the favorable substrate on which this syndrome makes its appearance. Renal failure is not a necessary accompaniment. Possibly some degradation product of mecamylamine causes the nervous excitation in these few patients, especially since the camphane nucleus may be associated in derivatives with excitatory properties. Knowing of this syndrome we do not believe it constitutes a serious handicap to the use of the drug.

Ecolid is a good blocking agent with regular absorption (Plummer and associates[10]) studied clinically originally by Grimson and Winsor. Its dosage is small, average maintenance being 50 to 100 mg. b.i.d. So far we have seen no complications as the result of its use but we must remember that hexamethonium was used much more extensively before the hexamethonium lung disease appeared. Patients are relatively easy to handle when Ecolid is used. We use it in our severe and malignant hypertensives and only occasionally in those with the more moderate variety.

Both mecamylamine and Ecolid exhibit the usual beneficial effects on the decompensated hypertensive. With a fall in pressure compensation often appears without use of digitalis.

I don't wish to sound negativistic but I think it better to point out some of the difficulties that you as physicians are going to face in the daily use of these drugs. Clearly, they are a useful addition in the treatment of some types of hypertension, but they have serious limitations and these must be recognized lest a wave of nihilism engulf their use completely. This has happened to other drugs. We owe much to Smirk of New Zealand for the skill and conviction with which he demonstrated how to use these drugs and to Paton for their introduction.

Much more needs yet to be done to understand why the ganglion blocking agents fail in so many cases, why refractoriness develops and why supine pressure is often so little affected. We have not yet learned how to exploit "exercise hypotension." I cannot feel content to count the limited blessings of ganglioplegics without a very uneasy glance at their side effects and the long term results of widespread ganglion blockade.

Reserpine

The problems of reserpine have been so adequately described (Vakil[11]; Wilkins[12]), I think I can safely pass over it with a few notions about its use in hypertensives. I have already pointed out there are still those who find it has no effect on blood pressure and others that it lowers pressure "significantly" in some 70 per cent of patients.

We have convinced ourselves that reserpine in doses of about 0.25 to 1 milligram exhibits the same variability of effect as all other antihypertensive drugs. Nor are we able to predict which patients will show a good hypotensive response. It is purely trial and error just as is dosage. Despite all of the words used so far to describe the cerebral pharmacology of this drug, what information there is has been of little

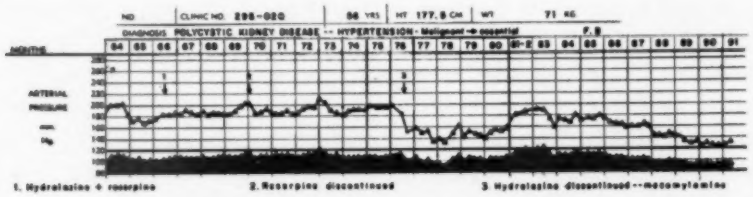
DIAGNOSIS POLYCYSTIC KIDNEY DISEASE -- HYPERTENSION - Malignant → essential
ARTERIAL PRESSURE
1. Hydralazine + reserpine
2. Reserpine discontinued
3. Hydralazine discontinued -- mecamylamine

Figure 3.—Failure of hydralazine and reserpine to control blood pressure adequately but successful use of mecamylamine. At (3) mecamylamine was started.

use in treatment of patients. The drug has a very prolonged action yet isotope studies show it to be rapidly metabolized; 30-40% appears in the urine as trimethoxybenzoic acid within four hours.

Combining reserpine with other drugs such as Ecolid or mecamylamine allows reduction of the dose of the ganglion blocking agent in some patients. In others, combined therapy is completely ineffective.

Occasionally the drug has seemed helpful in preventing the tachycardia, headache, flushing, etc., which may result in the first few weeks of administration of hydralazine. But again there is no regularity in this action.

Although reserpine is believed to be completely and regularly absorbed by mouth, we have given it intramuscularly to see if the effects differed. When 1 mg. is given in this way blood pressure may be profoundly lowered while, given by mouth the hypotensive effects may be small. But single parenteral administration gives no clue as to whether chronic administration by mouth will effectively lower arterial pressure. We have no reasonable explanation for this observation.

Brodie and his group have presented strong evidence suggesting that reserpine acts by liberating serotonin from the brain, which is then destroyed by amine oxidase. Shaw and Woolley[13] have prepared a large group of serotonin competitors one or two of which are said by Wilkins[14] to have an antihypertensive and reserpine-like action. This is an interesting line of thought and one well worth investigating.

Considering the amount of reserpine currently consumed, the number of toxic side effects must be small. On the other hand, some take an entirely too optimistic point of view. Everyone who has used reserpine has seen severe drowsiness, serious mental depressions, parkinsonism and other more minor disturbances (Freis[15]). These should be watched for and should not be dismissed lightly. The thought that these

drugs should be used for "nervousness", "tension", and all manner of ill-defined states, without careful attention of a physician seems to me nonsense. We have no experience with Feinblatt's[16] suggestion that 8 mg. of ephedrine combined with 0.1 to 0.2 mg. of reserpine relieves most of the side effects.

Reserpine can be valuable in the most varied types of hypertension. Wilkins suggested its use in the very early cases and yet Robert Platt finds it useful in malignant hypertension; a more diverse substrate could hardly be imagined.

Tranquilizing agents other than reserpine have not been used by us to any large extent. We have tried a combination of chlorpromazine with mecamylamine or Ecolid with no striking success. The effect seems purely additive. Patients with severe cerebrovascular disease and mental disturbance have definitely been benefited by chlorpromazine as have some with uremia.

Hydralazine (Apresoline)

This drug has now been widely used for about six years, yet there is still much disagreement about its value. Such able clinicians as McMichael, Smirk and Moyer find it of little use. This has not been our experience nor that of many others. In about one quarter of our patients blood pressure was reduced to normal and in another quarter diastolic pressure was reduced to 100-110 mm. Hg when this drug was used alone. The patients all had severe hypertension. I have no explanation for the failure of others to have at least some good results except possibly the care and persistence with which it is given in our Clinic. Almost all of our patients have had long periods in the hospital where new drugs are being studied and I suspect this accounts for much of the diversity of the results when compared with patients given drugs as out-patients. Most of our patients measure their own blood pressures when they are at home.

The initial side effects of Apresoline often discourage patient and physician alike from continuing with the drug. They may last for as long as eight weeks. During this period reserpine and/or antihistaminics are at times of value in preventing or lessening some of the side effects and allowing the dosage of Apresoline to be raised to between 600 and 800 mg. in a shorter time. After the maximum dosage and response have been attained we reduce maintenance dosage to between 300 and

400 mg.

We[17] with Schroeder[18] described in a few patients a fascinating new syndrome associated with administration of large doses of Apresoline. One part of the syndrome resembles early rheumatoid arthritis and the later and severer form acute systemic lupus erythematosus. The condition is reversible. To me its greatest interest and importance lies in the fact that experimentally a known chemical agent has produced a collagen disease for the first time. Comens,[19] in Schroeder's laboratory, has elicited a lupus-like syndrome in dogs fed Apresoline for four months. Curiously, others seem unable to get the same results. While these observations are of the greatest interest from the point of view of theory of collagen diseases, too much should not be made of them from the practical clinical viewpoint. The physician aware of the syndrome is forewarned and may avoid it altogether.

Schroeder, Morrow and Perry[20] in particular, have been strong advocates of combining Apresoline with hexamethonium, finding a synergistic action between the two drugs and an extraordinarily high percentage of success with the treatment. Others have confirmed and denied these claims. We have not been able to convince ourselves that any true synergism exists either from laboratory experiments or from bedside observation. Some of our patients have done better on combined treatment than on each drug alone. We continue to believe that some patients do not respond satisfactorily to one or the other drug and that combining this agent with another does not improve the response. But when each alone is shown to be useful, then a combination may be more successful. We have been accused of opposing combinations of drugs and this is true to the extent that we do not believe drugs should be given when their usefulness in an individual patient is unproved. So many hypertensives, for reasons entirely unknown, fail to respond to one or another drug. We have also vigorously opposed sale of combinations of drugs which make dosage regulation of the individual drugs impossible.

Six years' experience (Taylor, Corcoran, Dustan and Page[21]) with Apresoline leaves us convinced that, when used carefully and with cautious persistence, it is a valuable antihypertensive drug compared with others currently available. It often may be used successfully in combination with other measures. As a treatment, like all other antihypertensive treatments, it leaves much to be desired.

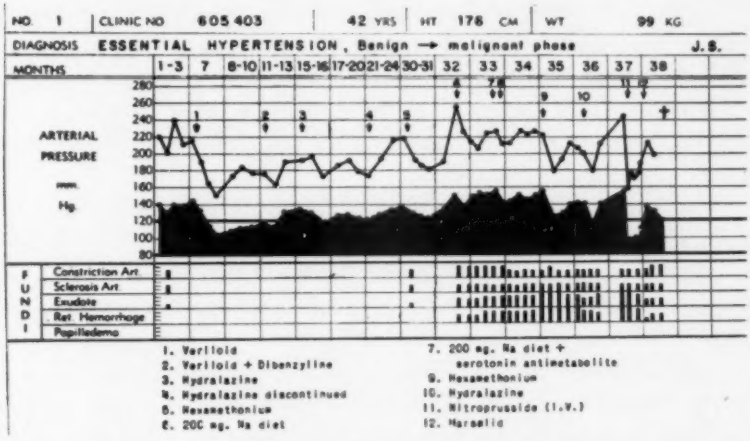

Figure 4.—Failure of a variety of antihypertensive agents to control blood pressure in a hospitalized patient. The following measures were tried:

1. Veriloid
2. Veriloid + Dibenzyline
3. Hydralazine
4. Hydralazine discontinued
5. Hexamethonium
6. 200 mg. Na diet
7. 200 mg. Na diet + serotonin antimetabolite
9. Hexamethonium
10. Hydralazine
11. Nitroprusside (I. V.)
12. Marsalid

Failures

Failures of treatment are an unpopular subject for discussion (as I have found[22]) yet to me what is behind failure may give the clue to success. Since about one-half of the severe hypertensives fail to respond satisfactorily for one reason or another, a great deal of attention should be given to these partial, or complete, failures. It is much pleasanter to recount one's successes but I shall be the devil's advocate and for the time being "raise the devil" to emphasize this aspect of current practice. As my first dart I think it fair to say that if you have no failures in your practice you will not recognize your true successes either. In short, study of your patients is inadequate.

Let me give you an example of one of our failures, a patient who spent most of his days under study in our hospital with almost nothing to show for it—not even a bill. His response to everything we tried was inadequate; intravenous infusion of sodium nitroprusside was the only measure that kept his arterial pressure down. Reserpine was not available at the time so he had no trial of this drug. It seems to me profitable to examine this chart carefully.

Failures are mostly of four sorts: 1) despite rigid adherence to treatment no response occurs to any of the measures employed; 2) the response is good but transient; 3) the response is poor but the reasons for it are clear; the patient takes treatment only when the spirit moves him and evidently the spirit is weak; 4) the side effects of the drugs are too disabling.

This always brings me to the point that until we know more of the mechanisms which are keeping the arterial pressure up, any thought of specific treatment is out of the question. We shall continue our groping empiricism until renal, neurogenic, cardiogenic and endocrinogenic hypertension become more than just words.[23] The uncovering of mechanisms in hypertension has failed to fire the imagination of scientists for the most part, hence progress is painfully slow. Correspondingly, too great optimism in our appraisal of treatment will only put off the day when treatment will be tailored to underlying mechanisms. Not to make an invidious comparison, but I doubt that "hot leads" in the field of cancer would receive such parsimonious interest as in the field of hypertension.

The Coming Era of Arteriosclerosis

Perhaps one of the most cogent arguments in favor of the view that antihypertensive drugs are prolonging patients' lives is the appearance of more and more vascular diseases. In the past few years we have been greatly impressed by the numbers of our patients treated for long periods who now show advanced arteriosclerosis, especially of the cerebral vessels.[24] More and more behavioral problems and frankly psychotic episodes are troubling us. Autopsy reveals widespread and severe atherosclerosis.

The manifestations of thrombosis and hemorrhage seem to come in attacks constituted of several strokes in the course of a few weeks interspersed with days of psychotic behavior or long periods of semiconsciousness. As Dr. Dustan expresses it, "the patients seem to be coming apart at the seams."

We are very much puzzled to know the cause for the extreme severity of the atherosclerosis. While we cannot prove it, the era now upon us seems quite different from that of ten years ago, due, I think, to the prolongation of life of the hypertensive by lowering his arterial pressure without correspondingly effective treatment of the vascular disease.

Conclusions

I hope my remarks on the treatment of hypertension will not be taken as nihilistic, because as many of you know, I am a chronic optimist. I would have to be to have stayed in this field for 26 years. Success in many aspects has been phenomenal, especially when one realizes that we started with some first rate misconceptions, no good experimental methods and no treatments worthy of the name.

Treatment today is comparable to the treatment of diabetes 30 years ago. It requires endless patience and far more time than most patients or physicians are willing to give. It is not a disease easy to treat and it is becoming more difficult to treat well as time goes on.

Enough patients with severe hypertensive disease are now being kept alive so that clinical manifestations of the associated vascular disease are looming larger and larger. Certainly 15 years ago we did not see the bizarre mental and morphological disturbances we are now seeing due, chiefly, to keeping patients alive so much longer. Cerebrovascular disease is becoming quite as important to treat as it is to lower blood pressure. A new spate of problems is upon us and a fresh approach needs to be taken. But let me emphasize again that while we all feel overwhelmed by new problems, the old ones are still far from satisfyingly solved. We still need better methods to lower blood pressure and to keep it down. We still must find out why we fail so often. We still must find the mechanisms causing the elevated blood pressure. We have not been able to buy success cheaply and we must not count on it in the future. Let us keep clearly in view the successes but also the failures which constitute the fabric of progress through research.

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PHYSIOLOGIC CONSIDERATIONS AND CLINICAL INDICATIONS FOR CARDIAC SURGERY*

The Wesley M. Carpenter Lecture

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WHEN one has the privilege of delivering a named lecture, the stimulus is present to learn something of the life and times of the man whose name designates the lectureship. I have learned that Wesley Mennen Carpenter was an outstanding medical journalist or reporter, as well as a teacher in medicine and pathology at the Bellevue Hospital three quarters of a century ago which in turn, to give an historical perspective, would be three quarters of a century after the first medical journal to be published in America, the *Medical Repository*, was launched in this city. The information is available that Dr. Carpenter, just 49 years of age, was found dead in bed the morning of January 7, 1888, without preceding illness. A postmortem examination was done and disease of the kidney was alleged to be the cause of death. Apparently the records of that postmortem examination are no longer extant. One can only conjecture whether heart disease—coronary sclerosis—might not have been the *actual* cause of death.

Amongst the medical offices held by Dr. Carpenter was that of corresponding secretary to The New York Academy of Medicine, and in tribute to this society he left $5,000 to support an annual lecture. Whether or not this bequest resulted in grievous harm to his estate, I do not know, but 13 years later contributions were being received to allow his widow to enter a home, and the lecturer that year, Dr. Abraham Jacobi, graciously returned his stipend to that fund.

I was intrigued to review the titles and general context of the past 65 Wesley M. Carpenter lectures as they have reflected the special

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medical problems and interests of the years. The subject of my lecture is appropriately consistent with that general theme, concerning, as it does, several of the pressing current problems in practice today. The title, "Physiologic Considerations and Clinical Indications for Cardiac Surgery," was suggested by your committee with the admonition that my remarks should be practicable and of use to the practicing physician.

Under the general topic of physiologic considerations, there could be three approaches: 1) a critique of special techniques, 2) an analysis of a special hemodynamic state, as pulmonary hypertension of varied cause, and 3) an assessment of disturbed function related to a specific anatomic lesion. Under the topic of clinical indications for surgical treatment, the main problems concern the identification of culpable defects and some prediction as to whether they are surgically remediable. In addition, emphasis must be placed on the question as to what extent clinical and hemodynamic data may separate and quantitate the respective contributions of mechanical defects and myocardial dysfunction (failure) in circulatory disability, and to this problem an adequate answer may not be forthcoming.

Patent Ductus Arteriosus

With due reverence to the historical sequence of the great surgical accomplishments for heart disease in our era, patent ductus arteriosus should be mentioned first. The physiologic aberration in patent ductus is now well known, in the average case about 50 per cent of the left ventricular output being shunted from the aorta into the pulmonary artery, and the pulmonary arterial pressure approximating normal values. Surgical indications are usually present with the establishment of the diagnosis in all typical cases, except perhaps in the aged. In infancy the typical murmur may be only systolic in time, and this syndrome should be now well recognized by the profession. Likewise, the clinical picture of a "reversing ductus" should now also be well known; in its far-advanced form the feet may be more cyanotic than the hands. Less advanced forms may be recognized by the difference in oxygen saturation of blood in the radial and femoral vessels and by the early appearance of dye, injected into the pulmonary artery, in the femoral artery as compared to its arrival time in the radial artery. These cases of patent ductus with a right-to-left shunt and without a significant left-to-right shunt are believed nonsurgical.[1]

Concerning the differential diagnosis of patent ductus, the usual mimicking lesions are 1) aortic-sinus aneurysm with rupture, 2) juxta-valvular aortic pulmonary fistula and 3) ventricular septal defect with aortic insufficiency. The first two defects are operable but require special surgical techniques and it is for this reason that accurate diagnosis is so desirable. When the continuous heart murmur is atypical in location or character in adults, the heart greatly enlarged, or pulmonary hypertension suspected, cardiac catheterization is usually indicated and the data may give support to the clinical suspicion of one or another of such anomalies. It may not need mention, but the laboratory data may not designate the anatomic defect accurately; for instance, the hemodynamic data of a case of ruptured aortic-sinus aneurysm might fit just as well a case of ventricular septal defect and mild infundibular stenosis. Parenthetically, it seems remarkable that severe symptoms and ultimately death may result from such small orifices in an aortic-sinus aneurysmal sac.

Coarctation of the Aorta

In coarctation of the aorta, the hemodynamic state of hypertension in the upper part of the body and of reduced systolic pressure and "a saw-tooth pattern" in the femoral arterial pressure records are established as characteristic but these are not needed for diagnosis. The clinical indication for surgical treatment in the usual case is contingent only on the diagnosis. Special diagnostic techniques, as aortographic examination, are rarely indicated. The syndrome of left-heart failure in infancy related to coarctation has been well publicized, and although conservative therapy has been recommended by some, my advice is "surgery," and the results in our clinic have been excellent. One worries about the coexistence of endocardial sclerosis and other defects, but these are uncommon.

The not rare defects associated with coarctation are patent ductus arteriosus (either above, opposite or below the stricture), subaortic stenosis and aortic insufficiency. Such lesions may usually be suspected clinically, and in the instance of patent ductus, cardiac catheterization is indicated primarily to determine pulmonary vascular pressure and resistance. In some instances in which the ductus is situated opposite the coarctation, it may serve as a collateral channel across the aortic obstruction. When a left-to-right shunt is present and the pulmonary

vascular resistance does not exceed about four times normal value, surgical reconstruction of the aorta with closure of the ductus still may be advised.

Atrial Septal Defect

In atrial septal defect, phenomenal degrees of transatrial shunts from left to right may occur, and the pulmonary vascular resistance is usually normal or subnormal. The clinical indications for surgical correction now are ever-widening to include most cases—certainly nearly all cases in which the lesion may be *clinically* diagnosed. We still catheterize these patients with the wish of helping the surgeon, particularly in the exclusion of anomalous pulmonary venous connections. Of particular value in this regard are dye-injection studies—by injection of dye either into the pulmonary vein, labeling the blood therein, or into the respective pulmonary arteries to determine abnormal patterns of pulmonary venous drainage.[2]

Besides the anomalous extracardiac pulmonary venous connections, there are three clinicopathologic states associated with an atrial septal defect that deserve recognition here: first is one my colleagues and I term, colloquially, "superior vena cava syndrome," second is common atrioventricular canal and third is acyanotic total anomalous pulmonary venous drainage. All of these defects are operable under favorable circumstances.

Superior Vena Cava Syndrome

By the superior vena cava syndrome is meant the drainage of one or more pulmonary veins into the base of the superior vena cava, and immediately beneath the caval orifice there is an atrial septal defect. A curious facet of the physiologic state may be the partial flow of blood from the superior vena cava into the left atrium, again a feature readily demonstrable by the dye-injection techniques.

Common Atrioventricular Canal

Under the appellation, "common atrioventricular canal," we include that form of atrial septal defect called "ostium primum defect" by others; physiologically and clinically it is interesting because of a sometimes associated mitral cleft in the mitral valve with insufficiency, and the not infrequent small left-to-right shunt at the ventricular level in

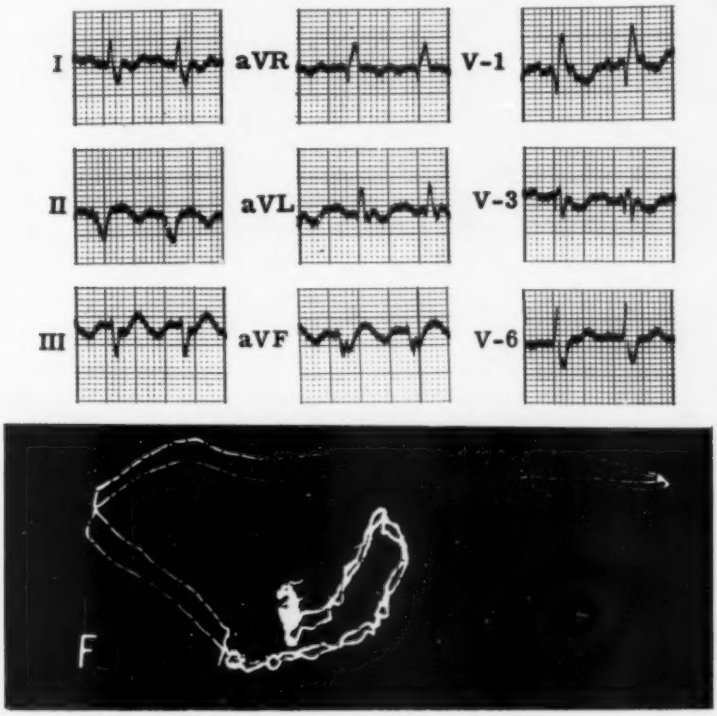

Figure 1—Electrocardiogram of patient with common atrioventricular canal. For discussion of record see paper by Toscano-Barbosa and associates.[3]

supplement to the larger transatrial shunt. Correction of the condition necessitates, first, the exclusion of gross mitral incompetence and, second, a special surgical approach, which, in our clinic, consists of repair under direct vision utilizing an artificial heart-lung apparatus.

Of all the unusual diagnostic problems in congenital heart disease, I know of none in which the electrocardiogram may be of greater value than in this condition of common atrioventricular canal.[3] In the traditional terms of scalar lead interpretation there is partial right bundle-branch block and left axis deviation (Fig. 1). A frontal-plane vectorcardiogram may be constructed or directly recorded and is likewise characteristic. The vector displayed in the frontal plane rotates counterclockwise, and the QRS loop is either mainly superior to, or horizontally disposed about, the iso-electric point. The electrocardiogram (or vec-

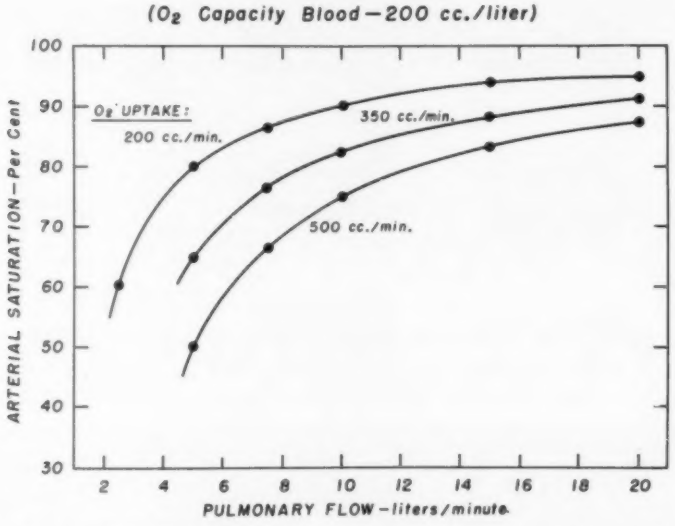

Figure 2—Calculated arterial oxygen saturations in total anomalous pulmonary venous drainage in relation to the rate of blood flow and the assumed rate of oxygen consumption. For method of determination see paper by Burchell.[4]

torcardiogram) is modified by the degree of pulmonary hypertension or of left ventricular hypertrophy, but the basic pattern remains the same. This type of tracing has not yet been observed in patients with atrial septal defect and *acquired* mitral insufficiency.

Total Anomalous Pulmonary Venous Drainage

Only recently has it been realized that when the pulmonary veins drain anomalously to the right side of the heart the patient may not only survive to adulthood with little disability, but also manifest little or no cyanosis. The presence or absence of cyanosis depends mainly on the pulmonary flow; when this flow is at a high level, the arterial oxygen saturation is also quite high, and even with the exercise this cyanosis may not be perceived (Fig. 2). One would expect that one laboratory feature of total anomalous pulmonary drainage would be identity of the saturations of the blood in the pulmonary artery and aorta. Of some physiologic interest is the finding in some cases that pulmonary arterial oxygen saturation may be slightly different than that of aortic blood. Such patients may closely resemble clinically those with the usual atrial

septal defect with a high left-to-right shunt.[4] Surgical therapy may be successfully applied, utilizing open cardiotomy and a cardiac bypass.

Pulmonary Stenosis

The clinical picture of isolated pulmonary stenosis, i.e., pulmonary stenosis with an intact ventricular septum, is sufficiently characteristic for the diagnosis to be made without cardiac catheterization, and the electrocardiogram usually gives adequate evidence of the severity of the stenosis, i.e., the right ventricular systolic pressure. The main problem remains in regard to the nature of the stenosis; whether valvular or subvalvular or combined. Cardiac catheterization records do not necessarily make a clear distinction although a normal valve area is more readily recognized than a normal subvalvular zone. This fact may be best emphasized by the result of pressure records at the time of surgery where the subvalvular obstruction is only hemodynamically apparent after the valve has widely opened. That this obstruction in the infundibular area is due to muscular contraction in some cases is illustrated by the recording of a marked pressure differential across it, even when the surgeon has been able to pass his finger through the area with relative ease. These physiologic findings are the basis for my opinion that cases of isolated pulmonary stenosis are best surgically treated by open cardiotomy. The exact right ventricular pressure level at which surgery is indicated is still debatable. As a working rule, it should be above 80 mm. Hg with a normal cardiac output.

When pulmonary stenosis is associated with a ventricular septal defect, it has been usually thought that the condition commonly would be associated with cyanosis—a tetralogy of Fallot. It should be recognized that acyanotic patients with this combination of lesions, a "pink tetralogy," if you will, are not uncommon, and it is doubtful if the pathologist could always predict from examining the heart, whether the patient had been cyanosed or not, i.e., whether the ventricular shunt had been from right-to-left or left-to-right. The results of intracardiac complete repair to date in the cases of left-to-right shunt have been, in general, better than in typically cyanotic tetralogy patients.

When pulmonary stenosis is associated with cyanosis, it is not possible to predict with accuracy whether the shunt is at the atrial or ventricular level. The distinction is readily made by dye injection techniques if catheterization is done, but if the therapeutic approach is that of

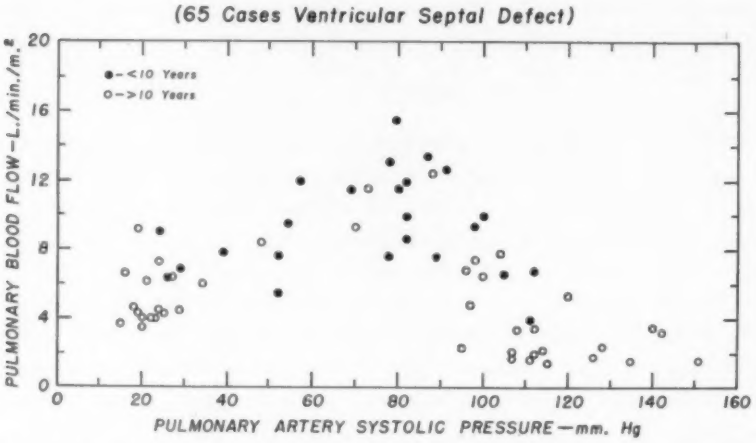

Figure 3—The relation of pulmonary blood flow to pulmonary systolic pressure in ventricular septal defect, from data in the cardiovascular laboratory of the Mayo Clinic. The points to the right where pressures are high and flows low represent patients who were cyanosed.

open cardiotomy with direct vision repair, the preoperative differentiation may not be necessary.

Pulmonary Vascular Resistance

The clinical problem presented by patients with ventricular septal defects is more frequently intimately related to the associated pulmonary vascular state than is any other congenital defect (Fig. 3). The associated pulmonary vascular changes determine not only operability, that is, acceptable hospital mortality, but the final surgical accomplishment as well. It is not logical to repair an intracardiac defect if the operation leaves the patient with severe and perhaps progressive pulmonary hypertension.

Experiences with patent ductus and atrial septal defect associated with pulmonary hypertension have indicated that there may be both fixed and dynamic factors in the pulmonary vascular resistance, and one could not predict accurately in these cases what the pulmonary pressure might be following the exclusion of a left-to-right shunt. In some cases, the increased pulmonary resistance has apparently been rather fixed as illustrated by the adult patient with atrial septal defect whose preoperative and postoperative hemodynamic profiles are given in Table I.

TABLE I.—EXAMPLE OF CASE IN WHICH INCREASED PULMONARY RESISTANCE HAS BECOME RATHER FIXED

	Pulmonary artery		
	Pressure, mm. of Hg.	*Flow, l./min.*	*Total resistance, dynes sec. cm.$^{-5}$*
Preoperative	65/20	6.3	560
Postoperative (11 mo.)			
Rest	38/18	4.5	435
Exercise	57/27	6.7	450

TABLE II.—EXAMPLE OF POSTOPERATIVE DECREASE IN PULMONARY VASCULAR RESISTANCE

	Pulmonary artery		*Resistance, dynes sec. cm.$^{-5}$*		
	Pressure, mm. of Hg	*Flow, l./min.*	*Total pulmonary*	*Arteriolar*	*Shunt, %*
Rest	83/52	10.3	480	380	60
Exercise	110/69	11.8	—	—	10
Breathing 100% oxygen	55/35	16+	210	155	—
Postoperative (7 mo.)					
Rest	38/14	9.5	190	130	0

An unusual case, in which a postoperative decrease in pulmonary vascular resistance occurred in a woman 28 years of age with patent ductus arteriosus, is portrayed in Table II. As demonstrated in this case, the breathing of 100 per cent oxygen may decrease pulmonary vascular resistance, the pressure dropping and the flow increasing. This is a frequent phenomenon but not an invariable one; when in the presence of severe pulmonary hypertension it is *not* observed, I believe it is an unfavorable omen as to general operability and regression of the hypertension.

In another patient, aged 13 years, with patent ductus arteriosus, the cardiac catheterization data showed that the pulmonary arterial and radial pressures were nearly equivalent but that a large left-to-right shunt was maintained. At the time of operation, pressure in the pul-

TABLE III.—EXAMPLE OF ACCELERATION OF PULMONARY VASCULAR CHANGES, ATRIAL SEPTAL DEFECT

	Pressure, mm. of Hg					
	Right ventricle	*Pulmonary artery*	*Flow, l./ min.*	*Resistance, dynes sec. cm.$^{-5}$*	*Systemic Flow, l./min.*	*Radial oxygen saturation, %*
1949 (age 22)	67/12	30/21	12.0	160	5.0	95
1952	81/20	—	12.6	—	6.3	90
1955	97/14	106/38	7.0	685	6.2	93

TABLE IV.—SURGICALLY TREATED PATIENTS WITH ATRIAL SEPTAL DEFECT AND PULMONARY HYPERTENSION

Case	*Age, years*	*Pulmonary pressure, mm. of Hg*	*Pulmonary flow, l./min.*	*Arterial saturation, per cent*	*Resistance, dynes sec. cm.$^{-5}$*	*Post-operative study*
1	49	105/31	5.5	92	800	No
2	22	106/38	7.0	93	670	Died
3	32	66/22	12.1	97	538	Yes
4	44	71/23	6.4	97	560	Yes
5	23	86/33	7.0	94	560	Yes
6	24	70/38	10.6	89	365	Yes

monary artery dropped from 112/72 to 82/46 and yet, five and a half months later, it was 45/10, in millimeters of mercury.

A word or so is deserved concerning the rate of progression of pulmonary vascular changes in patients with left-to-right shunts. Apparently in many cases the condition is hemodynamically static, but, in a few, pulmonary vascular obstructive changes may enter an accelerated phase. For example, a girl with atrial septal defect followed the course shown in Table III. This patient died several days after surgical closure of the atrial septal defect. The high preoperative venous and right ventricular diastolic pressures are to be noted.

To me, it seems premature at this time to set up rigid laboratory specifications for operability in patients with atrial septal defects—specifications based, for instance, on calculated pulmonary resistance. Patients who have heart failure will be operated on with very high risk, and

those who have only right-to-left shunts are considered inoperable. One successful surgical procedure has been performed on a woman 49 years old with a calculated pulmonary vascular resistance of 800 dynes seconds centimeters^{-5} while she was breathing air. Her condition was considered borderline or even unsuitable for surgical treatment, but the operation was finally advised with some hope of helping her, as the left-to-right shunt increased from 37 to 71 per cent and the calculated pulmonary vascular resistance dropped to 350 dynes seconds centimeters^{-5} when she was breathing 100 per cent oxygen. Since the operation, the patient has shown marked clinical improvement with nearly complete disappearance of her previous disabling fatigue and dyspnea (case 1, Table IV).

Ventricular Septal Defect

In ventricular septal defect it would be reasonable to believe that it is mainly the size of the aperture relative to the aortic orifice that sets the pressure gradient across the defect, which in turn determines the shunt. However, when right and left ventricular pressures are equivalent, there is a marked variation in the amount of shunt, with the pulmonary and systemic vascular resistances determining the volume of the shunted blood. It was a surprise to observe patients with tremendous defects in the ventricular septum, indeed the approximation of a single ventricle, who had pulmonary pressures that were lower than the aortic pressure. These data reflect the very low pulmonary vascular resistance relative to the systemic resistance in such patients.

In past years the belief that, in the case of single ventricle, the saturation of the blood in the pulmonary artery was identical with that in the aorta rested on sound logic. There is, however, a discrepancy in such a prediction from the morphology and the observed physiologic facts, as the saturation of the blood in the aorta may be slightly different from that in the pulmonary artery. In infants, particularly, as incredible as it might seem, it occasionally may be most difficult to differentiate the case of single ventricle from that of large ventricular septal defect with bidirectional shunting by the techniques of cardiac catheterization including dye injections. In such problem cases of single ventricle the electrocardiogram may be of great help in indicating the absence of a thick right ventricular chamber. It is of clinical as well as pathologic interest to note that these young patients with a single ventricle and a

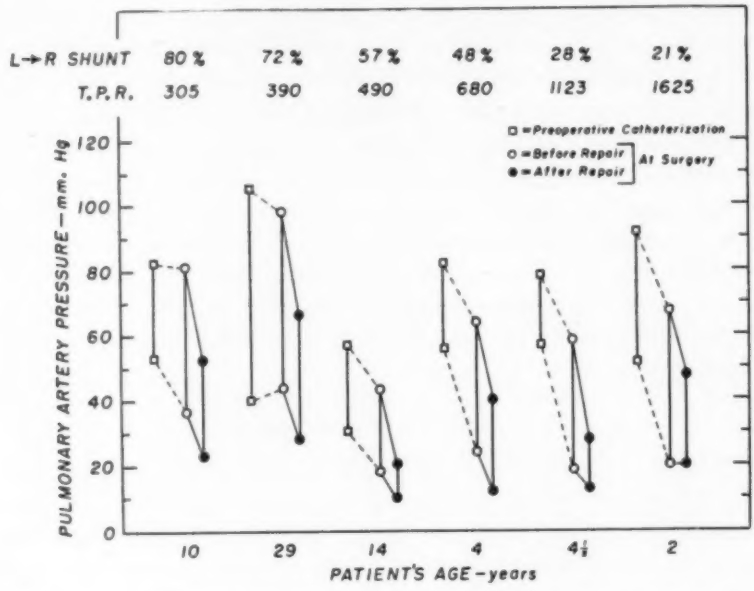

Figure 4—Pulmonary arterial systolic and diastolic pressures showing the immediate changes consequent to the closure of a ventricular septal defect in the operating room, as compared with the preoperative catheterization figures. The patients made up the first group of successful operations in which complete data were available. The significance of these figures is discussed in the text.

big pulmonary artery usually have the great vessels transposed.

In the broadest aspect of the surgical approach to ventricular septal defects, the operation is for the purpose of closing off a left-to-right shunt. When the shunt is reversed (that is, becomes a right-to-left shunt), physiologic theory and clinical hope would indicate the desirability also of closing the defect; clinical experience, the pragmatic school, if you wish, now dictates that it is a fatal course to follow.

Pulmonary pressures from a group of our early surgical cases of ventricular septal defect operated upon by Dr. J. W. Kirklin at the Mayo Clinic, unselected except on the basis that adequate data were available, do not show a postoperative change that could be quantitatively related to the preoperative catheterization data, such as the calculated left-to-right shunt or total pulmonary resistance (Fig. 4). These figures on pulmonary pressure after the surgical closure of the defect are more meaningful if I tell you that the shunt had been abolished and

the pulmonary flow was normal, as determined by dye-dilution curves.

The importance of the electrocardiogram in reflecting the long-time average hemodynamic state in patients with ventricular septal defect must be stressed. When the electrocardiogram does not show evidence of left ventricular enlargement but reflects mainly right ventricular hypertrophy, the overwhelming chances are that the condition is inoperable.

Acquired Heart Disease

In the tremendous field of acquired heart disease, only a few problems can be selected for discussion. I have chosen to dwell on the problems inherent in recognizing the predominant defect when stenosis and incompetence are coexistent in the mitral or the aortic valve, and on the problem of determining which valve is mainly at fault in a heart in which both aortic and mitral valves are involved. At times in this regard, one's efforts and accomplishments seem to take the form of a purely physiologic exercise rather than the avenue to successful diagnosis and therapy. However, one may uncover unsuspected hemodynamic aberrations that lend themselves to surgical treatment.

Mitral Stenosis and Insufficiency: My personal experience is greatest with disease of the mitral valve and with the results of surgical relief of mitral obstruction. Although a number of observers, including my colleagues and me, have recorded immediate drops of left atrial pressure on opening the valve orifice, there has been the universal experience that the early and late changes in hemodynamic measurements following mitral valvulotomy are indeed small as compared to the marked clinical gains. To me, this reflects the critical orifice size at which severe difficulty develops in patients with mitral stenosis. When, with mitral stenosis, mitral insufficiency is also present, the benefits of surgical therapy dwindle greatly in my experience. In this problem the determination of mitral-valve function by left-heart catheterization has added much to current knowledge. The degree of mitral incompetence may be gauged by the height of the ventricular pulse in the left atrium, by the recovery of dye from the left atrium after injection into the left ventricle, and by the contour and internal relationships of the dye-dilution curves.

Prior to the advent of techniques for left-heart catheterization, "wedge-pressures" gave much help in the diagnosis of mitral insuffi-

ciency. The basis for this depends upon the fact that when the cardiac catheter is advanced until it is wedged in a small branch of a pulmonary artery, pressures are obtained that accurately reflect the mean pressure and usually the pressure variations (contour) in the left atrium. When large ventricular pulses are evident in such wedge records, it strongly indicates the probability of mitral insufficiency. Studies in our laboratory by Dr. D. C. Connolly[5] led to the conclusion that discriminatory assessment was served best by relating the height of the V (ventricular) wave to the mean pressure, but it was only when the mean pressure was more than 20 mm. of mercury that the regression lines of the charted points of known cases of mitral insufficiency and of mitral stenosis diverged so that the chart became diagnostically of help. With increasing numbers of cases of combined stenosis and incompetence studied, there has been an increasing number of points falling between the lines.

A similar chart has been made from left atrial values for V wave and mean pressure, and in such a graph the cases of mitral stenosis and mitral insufficiency are likewise separated only at moderate or high values of mean left atrial pressure. Again, when the two hemodynamic faults, stenosis and incompetence, coexist, the height of the V wave usually reflects such a combined fault, with the charted value falling between the regression lines of the points of known pure mitral stenosis and of mitral insufficiency.

When one measures simultaneously the pressure in the left ventricle and left atrium and finds a diastolic gradient of 10 mm. of mercury or more that persists throughout the diastolic period, mitral block is evident. However, if the gradient is eliminated at the end of the diastolic period or there is ancillary evidence of associated mitral incompetence, then diastolic gradients as a measure of the valve orifice are much more untrustworthy. One would like to have, to determine either valve resistance or the size of the valve orifice as by the Gorlin formula, a measure of the total diastolic flow, which is the sum of forward flow and regurgitant flow.

Dye-dilution techniques have been utilized by Dr. E. H. Wood and associates in our laboratories in attempts to measure regurgitant flow. In the first place, it was noted that the normal time relationships of the arterial dye-dilution curve were disrupted when gross mitral insufficiency existed, the disappearance slope being flattened (that is, the rate of decreasing dye concentration following the peak concentration was

slow) relative to the build-up slope, with a resulting dye-dilution curve simulating that seen in left-to-right shunts. To draw a simile, and visualizing some dye being temporarily trapped as it flows back and forth between atrium and ventricle, one might call the curve a "shuttle curve" in contrast to the left-to-right "shunt curve" that is simulated. In addition to the abnormal disappearance slope, the peak concentration of the dye is less than expected for the existing cardiac output. As the normal range of values for the peak concentration in the radial dye curve subsequent to injection of the dye into the pulmonary artery is known, then the degree in reduction serves as an index of the severity of the mitral insufficiency. Korner and Shillingford,[6] observing these phenomena, mathematically analyzed their curves and found that the dye technique gave promise of accurate quantitation of regurgitant flow, though carefully pointing out the difficulties that are involved. Our experiences, still incompletely analyzed, with a group of cases of varying cardiac output and cardiac size indicate that for such a varying group of cases with mitral insufficiency there is little hope of exact quantitation but that approximations may be worth while.

It may be pointed out that sometimes the locus of the incompetent valve within the heart may be determined. For example, if the dye is injected into the pulmonary artery and samples are taken from both the left atrium and the radial artery, and if the disappearance slope is prolonged in the radial dye-dilution curve but not in the left atrial curve, then the "smearing effect" must be caused by something "downstream" to the mitral valve, that is from incompetence of the aortic valve. Care must be exercised in such an interpretation, as complete mixing of dye in the left atrium does not always occur. A second example would be the localization of the incompetent valve in the right side of the heart (that is, tricuspid valve) if the injection into the pulmonary artery resulted in an undeformed dye-dilution curve from the radial artery while the injection into the superior vena cava resulted in a deformed curve having a flattened disappearance slope.

A second way of utilizing dye to indicate mitral valvular incompetency is to inject it into the left ventricle while withdrawing blood from the left atrium (Fig. 5). One must have reason to believe that the tip of the catheter is in the left ventricle throughout the injection and that the catheter has not significantly altered valve function. The amount of dye regurgitated into the left atrium may be calculated, and surpris-

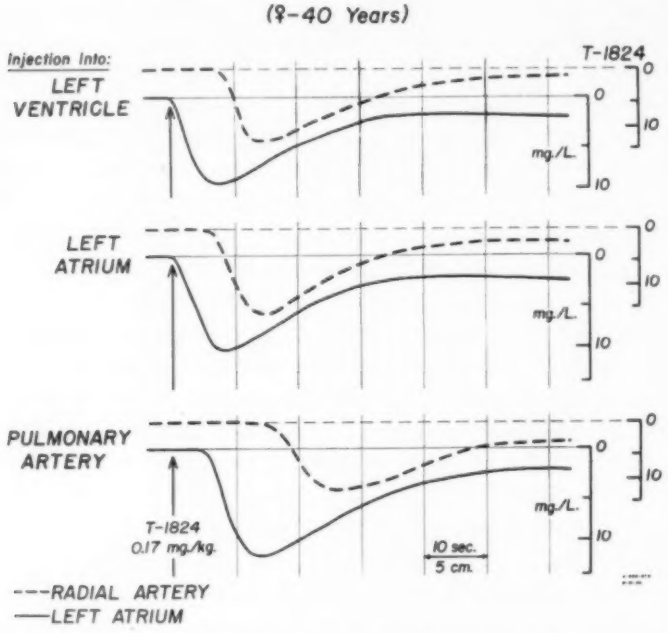

Figure 5—Dye-dilution curves from the left atrium and radial artery after injection of dye into the left ventricle, left atrium and pulmonary artery of a patient with severe mitral insufficiency. The peak concentration of the dye is less than normal and the disappearance slope, indicating the decreasing concentration of the dye relative to the build-up slope, is flattened or prolonged. When the dye is injected into the left ventricle, a large quantity appears immediately in the left atrium, indicating directly the gross mitral incompetence.

ingly high values may be obtained—values as high as 40 per cent having been obtained in patients whose insufficiency the surgeon had estimated as being of only moderate degree.[7]

A comparison of a number of these tests may be seen in Tables V and VI. Table V represents a group of patients operated upon for mitral stenosis, and Table VI represents a nonsurgical group in which the final diagnosis was mitral insufficiency.

Clinically, operation on the mitral valve is recommended when there is good evidence of "mitral block," with signs of pulmonary hypertension or episodes of pulmonary edema and progression in disability, preferably when all signs of active carditis have been absent for some years.

Aortic Stenosis and Insufficiency: The diagnosis of aortic stenosis

TABLE V.—SURGICALLY TREATED "MITRAL STENOSIS" WITH COMPLETE DYE STUDIES*

Case†	Clinical diagnosis	Early dye LV → LA	Disappearance slope	Wedge "V"	M	Left atrial "V"	AV gradient (0.1 second)	CI
1	MS	Trace	N	MS	37	MS	10	2.8
2	MS-MI?	Trace	N?	MS	22	MS	11	2.4
3	MS	O	N	—		MS	11	1.8
4	MS-MI?	++	N	MS-MI?	35	MS-MI	19	2.0
5	MS-MI	O	N	MI-MS	17	MS	11	1.9
6	MS	O	N	MI	24	MS	18	2.1
7	MS-MI?	+	N	MS	31	MS	18	1.7
8	MI-MS	+	N	—		MS	17	2.8
9	MI-MS	+	N	—		MS-MI	14	1.3
10	MI-MS	+++	+	MS	20	MS	24	3.1
11	MS-MI	++	+	—		MS-MI	8	1.5

* Abbreviations: LV, left ventricle; LA, left artrium; V, "V wave" height interpretation; M, mean pressure, mm. of mercury; AV, atrioventricular; CI, cardiac index; MS, mitral stenosis; MI, mitral insufficiency; N, normally related disappearance slope; +, ++, +++, amount of dye recovered from left atrium after left ventricular injection.

† In cases 1, 2 and 3 the surgeon assessed the condition of the valve as pure stenosis; in cases 4 through 9, as mitral stenosis with slight to moderate insufficiency; and in cases 10 and 11, as marked insufficiency. Left-heart catheterization was performed in all cases because of the clinical suspicion of possible insufficency associated with stenosis.

has become more difficult even with increasing knowledge of the variation of clinical signs. Left-heart catheterization has taught us a great deal and permits a diagnosis of aortic stenosis to be established on the basis of the recording of a systolic gradient across the aortic valve. However, when aortic stenosis and incompetence are coexistent, calculation of the severity of the stenosis is more difficult. In general, the presence of aortic insufficiency, as determined by a readily recognized aortic diastolic murmur, militates against the chances of successful surgical therapy aimed at relief of the stenosis. Aortic and peripheral arterial pulse contours are very characteristic when either pure aortic stenosis or pure aortic insufficiency is present, but when they are coexistent the pulse contours may not be discriminatory.

It has already been intimated that hemodynamic data may be difficult to use as measures of myocardial failure, and the clinical response to treatment with digitalis may be a better index to the presence of myocardial failure than are the data from a single isolated cardiac catheterization. A low systemic flow (reduced cardiac output) is generally a

TABLE VI.—MITRAL INCOMPETENCE (LABORATORY) WITH COMPLETE DYE STUDIES (Nonsurgical)*

Case	Clinical diagnosis	Early dye LV → LA	Disappearance slope	Wedge "V"	M	Left atrial "V"	AV gradient (0.1 second)	CI
12	MI-MS	++	++		13	MI?	4	2.9
13	MI	++	+	MI	31	MI	13	1.7
14	MI-MS	++	+		14	MI?	5	2.4
15	MI-MS	+	+?	—		MI 27	14	1.4
16	MS-MI	++	++	MI	29	MI?	8	2.4
17	MI	++	++	MI	26	MI	6	1.7
18	MI-AS	++	++	MI	21	MI	0	1.8
19	MI-MS?	+	0	MI?	7	MI?	0	2.2
20	MS-MI	++	+	MI	24	MI	7	2.2
21	MI	++	0	MS	31	MS	3	3.6

* Abbreviations are defined in Table V. The plus signs in the column *"Disappearance slope"* in Tables V and VI indicate the presence and degree of the abnormality in the dye curve.

counterpart of failure, as is an increased end-diastolic pressure in one or both ventricles, but these two features are not invariable or directly interrelated. For instance, in an occasional case of aortic insufficiency, the end-diastolic pressure in the left ventricle may be very high in the absence of signs or symptoms of failure.

Constrictive Pericarditis: In any cardiologic clinic one is certain to see ambulatory patients with distended neck veins, enlarged liver, and ascites who, one first suspects, may have constrictive pericardial disease, although enlargement of the cardiac shadow or absence of pericardial calcification may be placed in evidence against such a diagnosis. Occasionally, exploration may be required to exclude pericardial disease with certainty if other methods of diagnosis fail. Angiocardiography and cardiac catheterization may give useful clues but may not be definitive. The pressure contours in the various cardiac chambers that do characterize constrictive pericarditis may also occur in patients with amyloid heart, myocardial fibrosis and endocardial sclerosis.

COMMENT

In any final assessment of physiologic considerations in the selection of patients for surgical treatment, close cooperation of physician, surgeon and laboratory worker is essential, as they are so obviously inter-

dependent. In general, any specific laboratory test that is at odds with the clinical picture may need to be discounted. One may mentally wander to comment that, after each laboratory Prometheus has brought some new fiery and valuable gift for the use and advantage of the practitioner, the latter occasionally may well figuratively burn his fingers before he learns to use the gift correctly.

Conclusion

To conclude the Wesley M. Carpenter Lecture, it would be appropriate to quote from his writings a statement that would summarize some of the problems of today, albeit perhaps in a philosophical vein. Dr. Carpenter left no great medical manuscripts for posterity, but he did publish a small manual called *Index of Treatment* which apparently had considerable usage. However, failing to find a suitable statement in this text, I shall quote a philosopher who was teaching in his first academic post at the University of Minnesota in 1888 when Dr. Carpenter died, namely John Dewey, who stated that every portion of new thought puts that existent into peril—a statement which, I submit, is certainly as pertinent to the medical dogma expressed in this paper as to general philosophy.

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REPORT ON TRANQUILIZING DRUGS

BY THE

COMMITTEE ON PUBLIC HEALTH*†

OF

THE NEW YORK ACADEMY OF MEDICINE

THE Committee on Public Health was requested by the Commissioner of Health of New York City to ascertain whether the present widespread use of tranquilizing drugs constitutes a menace to public health. Subsidiary to that was the question whether the literature about the drugs sent by pharmaceutical houses to physicians contributed to improper use.

It is germane to inquire exactly which drugs are to be considered as tranquilizing drugs. However, it is not easy to arrive at a satisfactory definition. One definition which has been offered is that a tranquilizing drug is any drug given for the purpose of making a person feel better when he is tense. But the major difficulty in a clinical definition is the fine line between tranquilization and sedation. The tranquilizing drugs as a group are known commonly by other names. Professionally they are called ataractics. The lay press often refers to them as "happiness pills."

The tranquilizing drugs may be conveniently divided into two groups. The first contains drugs of the Rauwolfia alkaloid type. The second group comprises synthetic compounds. Each member of the latter group may bear as many as three different names: its full chemical name, a short and more convenient name, and finally, its proprietary name. For example, the full chemical name of one is 2-methyl-2-*n*-propyl-1, 3-propanediol dicarbamate. Its abbreviated name is meprobamate. It is marketed under at least two different proprietary names, Miltown and Equanil.

It should be emphasized that the tranquilizers are exceedingly useful drugs. Wide usage of them attests to their value. Originally they were utilized mainly in mental institutions in order to bring patients under control and make them more accessible to other therapy. It is asserted that they have greatly mitigated the problems of custodial care, reduced admissions, and have brought about earlier discharge of the patients.

Very soon, however, the drugs were prescribed in private practice for the many who were seeking relief from anxiety and tension. Their usage in this area has been on a gigantic scale. The American Psychiatric Association has stated that 35 million prescriptions for these drugs will be written in 1956, and that of ten compounds most frequently prescribed by physicians in 1955, three were tranquilizers. At the

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* Approved by the Committee on Public Health of The New York Academy of Medicine, December 3, 1956.

† Report prepared by Subcommittee on Tranquilizing Drugs, comprised of: J. Murray Steele, M.D., Chairman; Linn J. Boyd, M.D.; McKeen Cattell, M.D.; Hubert S. Howe, M.D. (Deceased, Feb. 4, 1957); Stephen P. Jewett, M.D.; M. Ralph Kaufman, M.D.; Asa L. Lincoln, M.D.; H. D. Kruse, M.D., Secretary.

present time 5 to 10 per cent of all prescriptions in New York City are for tranquilizing drugs and an increased percentage is anticipated.

In some minds this widespread use of tranquilizers in meeting everyday situations raises a question about the rationale underlying it. Anxiety and tension seem to abound in our modern culture and the current trend is to escape the unpleasantness of its impact. But when has life ever been exempt from stress? In the long run is it desirable that a population be ever free from tension? Should there be a pill for every mood or occasion? It has been noted that when the drug is used satisfactorily in an emergency, there is a tendency among some persons to regard more and more of life's situations as emergencies until the pattern results in everyday usage of tranquilizing drugs. Their use is said to be becoming more and more common among persons in certain occupations.

All drugs have a range of safety and recommended dosage. Many of them have side effects or produce reactions in a proportion of persons either at the recommended dosage or especially beyond that level. Hence, all new drugs are subjected to test. By accepted procedure, they are tested in the laboratory prior to their clinical use, next they are tested on patients under controlled conditions by a few clinicians, then they are released to the medical profession on an experimental basis for further clinical testing.

Like many drugs, the tranquilizers are not without their side effects and undesirable consequences. Kramer has reviewed the clinical reports of toxic effects produced by two of the tranquilizing drugs: chlorpromazine and reserpine. For the present purposes it is sufficient to summarize the untoward effects. Chlorpromazine, for example, has led to parkinsonism—fortunately reversible—, allergic dermatitis, constipation, diarrhea, jaundice, agranulocytosis, and torsion syndrome. As for reserpine, prominent among its side effects are the production of parkinsonism and the occurrence of severe depressive reactions, sometimes when the drug was administered as an anti-hypertensive agent, not for a psychiatric disorder. Its use may also be accompanied by a variety of other side effects.

In pointing to the need for additional precautionary steps in the marketing of reserpine, the Food and Drug Administration reviewed the recent evidence on the side reactions from the use of this drug. It stated: "Continued use of reserpine in doses of 0.32 mg. daily has been shown to increase gastric secretion and gastric acidity in a significant number of cases whereas daily doses of 0.25 mg. have not been shown to do so. Doses of 0.5 mg. daily for as short a time as two weeks produced this effect in most of the individuals tested and have resulted in massive gastro-intestinal hemorrhage or perforation of an ulcer. More important, reserpine in daily doses of 0.5 or 1.0 mg. produces severe depression in a significant number of individuals, and has precipitated a very considerable number of suicidal attempts, some of them successful. Many of these depressions have been severe enough to necessitate long-term hospitalization in psychiatric institutions."

Friedman and Marmelzat reported that adverse reactions following the administration of meprobamate included cutaneous, paradoxical cerebral, muscular and gastrointestinal effects. The cutaneous effects were chiefly purpuric with intense itching. Next in frequency was the production of excitement rather than the desired tranquilization. Severe diarrhea and temporary paralysis of the extra-ocular muscles producing diplopia also occurred.

Lemere has reported that withdrawal symptoms are sometimes experienced by patients taking meprobamate over a period of time. Originally he had believed that

no tolerance to the tranquilizing drugs ever developed. But as an addendum to his report, he cited the observation of the tolerance phenomenon in nine patients.

Such clinical reports on new drugs are valuable in pointing to levels of proper dosage. Furthermore, they reveal the nature and severity of side effects which may be encountered. At the same time they bring out contraindications. They may even point to the need for special cautionary statements on the label.

In a letter to pharmaceutical firms, the Food and Drug Administration has stated: "As the drug [reserpine] has been used more extensively it has become increasingly apparent that reserpine is not the innocuous substance it was first thought to be, that there are contraindications, and that the safe level for long term outpatient maintenance is lower than the originally recommended dosage schedule. . . . In the treatment of hypertension, or of anxiety states on an outpatient basis, it is the present consensus that the usual recommended maintenance dose should be 0.25 mg. daily. While doses up to 1.0 mg. daily may safely be recommended for the initiation of therapy, they usually should not be continued for longer than a week . . . it is believed that reserpine in daily doses above 0.25 mg. is contraindicated and in lower doses should be used with caution in patients with a history of mental depression, peptic ulcer or ulcerative colitis. Furthermore, physicians should be specifically cautioned with respect to the danger of depression. . ." Also, reserpine in neuropsychiatric use in higher strength ". . . should be discontinued approximately one week before instituting shock therapy, since it may result in increased severity of convulsions, respiratory difficulty, and other complications; . . . the possible dangers of hypotension and fluid retention should be borne in mind when large doses are used in debilitated patients or those with cardiac disease." It is to be noted that chlorpromazine likewise should not be used in patients showing symptoms of depression.

In view of the clinical reports on side effects and contraindications, it is important to determine whether there is any foundation to the concern that misuse of these drugs with undesirable effects creates a problem in public health. The answer to this question lies in whether there is evidence on several points: that both short-term and continuous use of the tranquilizing drugs without medical supervision is dangerous; that persons are using these drugs without medical supervision in an unwarranted or unrecommended manner; that such indiscriminate, unregulated and reckless use results in morbidity or mortality; and that the latter occurrences are on such a large scale as to justify concern over public health.

These are new drugs and clinical experience at this time is revealing but incomplete. It is limited to short-term use. Yet even from the limited observations it may be inferred that these valuable drugs are potentially harmful. As for the effects of prolonged, continuous use, nothing can be said at this time. But on the basis of the available clinical evidence, the Committee can conclude that there is a possibility that use of the drugs without medical supervision may be attended with danger.

It should be clearly stated that the magnitude of prescriptions for tranquilizing drugs does not prove that they are a menace to public health. Rather, the danger would lie in the use of them for both short and long periods without medical supervision, whether with or without prescription. Overdosage under these circumstances would be especially a hazard. This is the significant question: Is there access to these drugs and use of them without medical supervision? Presently the amount of these drugs being sold without prescription is not known. It is the considered opinion of the Department of Health that there has not been any great amount of

over-the-counter sale of them. Nevertheless, it is possible that persons now taking these drugs on prescription and benefiting from them distribute them rather widely among their friends and relatives.

However, the major source of misuse may be in excessive refilling of prescriptions without the physician's knowledge. Under the Sanitary Code of New York City there is no prohibition against refilling of prescriptions for these drugs. The patient may find such relief of his symptoms that he continues to take the medication long after the period originally intended by the physician. Thus it is the Health Department's impression that persons are getting prescriptions refilled without a physician's order, an entirely legal procedure in New York City. Certainly by this means the public does have access to the drug without medical supervision. Whether it has availed itself of this opportunity has not been definitely established.

The potential danger from misuse of these drugs and the opportunity for using them without medical supervision can be accepted. But additional evidence of another character is desirable before pronouncing the situation a menace to public health. What is needed is evidence of morbidity and mortality associated with their use. At present there are definite impressions but few facts; for, the data are difficult to obtain. Despite all the precautions in the preliminary testing of new drugs and the safeguards thrown around their issuance, it is the usual experience that the full effects of new drugs, both beneficial and detrimental, are seldom revealed until they have been used extensively over a period of time. This is particularly true of a drug that comes into wide and popular use shortly after its appearance. Hence the difficulty in amassing data on the morbidity and mortality associated with tranquilizing drugs arises from the very short time that they have been widely used. Widespread usage over a short period of time does not reveal the full effects of the drug. It is necessary to obtain more than a sample of short-term experience that is sufficiently large and varied. It is essential also to observe the effects of prolonged and continuous use. There is no substitute for time.

The New York City Health Department has some data which may allow provisional and presumptive inferences. In 1955 according to the records of the Poison Control Center, there were 12 cases of poisoning associated with the tranquilizing drugs as against 76 for the first 10½ months of 1956. In 1955 there were no fatalities associated with the tranquilizing drugs; for the first 10½ months of 1956 there have been two. In neither of these fatalities is there positive finding that the tranquilizing drug was the cause of death, although large amounts had been taken. No known suicide attempts associated with tranquilizing drugs were reported for 1955 as against 16 for the first 10½ months of 1956. It is usually not easy to ascertain suicidal attempts under any circumstances. It is particularly difficult to attach the precise responsibility of tranquilizing drugs. On the one hand, for the person bent upon self-destruction, that may be the method of choice. On the other hand, some of the tranquilizers may plunge the susceptible individual into a depression which leads him to select some other means of suicide. Admittedly this evidence on mortality and morbidity associated with tranquilizing drugs is far from conclusive in determining whether they constitute a public health problem. But at least they point to caution and constitute a warning.

Manifesting a concern over the dangers inherent in the casual use by the public of tranquilizing drugs for the relief of everyday tensions, the American Psychiatric Association through its Committees on Research, Therapy, and Public Information issued a statement condemning the practice. The Association expressed its enthusi-

astic recognition of the benefits derived from the development of the tranquilizing and other drugs for the treatment of psychiatric disorders over the past four years and listed the beneficial effects. But, they said: "Psychiatrists are at the same time concerned about the apparently widespread use of the drugs by the public for the relief of common anxiety, emotional upsets, nervousness, and the routine tensions of everyday living. . . . Casual use of the drugs in this manner is medically unsound and constitutes a public danger. The tranquilizing drugs have not been in use long enough to determine the full range, duration, and medical significance of their side effects. Use of these drugs is no more to be encouraged than use of any other drug except where proper medical diagnosis determines that a drug is indicated to maintain the life and functioning of a person. The prescribing of drugs for emotional illnesses carries with it an obligation for continuing appraisal and supervision by physicians fully aware of the psychiatric symptoms involved and the potentials of their course of development, alteration or remission."

By reason of the evidence on the side reactions from the use of reserpine, the Food and Drug Administration has suggested an upper limit for the recommended maintenance dose in the treatment of hypertension and a usual maintenance dose in the treatment of institutionalized psychotic patients. Since the two levels of dosage were different, it recommended distinctive statements on the label and the printing of declaration of the strength of the tablets in a different color from the rest of the label.

At the stage when there is widespread use of a drug, presumably much of it without medical supervision, when its full effects have not been determined, and when the evidence of associated morbidity and mortality points to the possibility of an increase but is so insufficient as to be indefinite and indecisive, it is difficult to predict whether a situation detrimental to public health will develop. Hence it is not easy to reach a decision during this early period as to whether further legal safeguards should be established. When there are only indications but insufficient evidence of potential dangerous effects on a large scale, it becomes a matter of choice between two courses. According to one viewpoint, it is better to act early before the data becomes overwhelmingly decisive. Even if anticipations of the worst are not realized, any hardships incident to the imposition of controls are counted as small cost when balanced against the high dividends of safety ensuing from precautionary measures. The opposing school is of the opinion that it is important to be certain that controls are essential for the management of a public health problem before action is taken. This view would counsel to defer controls until sufficient evidence of harmful effects on a large scale had been established. Perhaps this position is best epitomized in the phrase "watchful waiting."

The diametrically opposite histories of usage and control of two other groups of drugs, the antihistaminics and the barbiturates, are illustrative. It may be recalled that indiscriminate widespread usage of the antihistaminics with their undesirable side effects occasioned a considerable problem for a time, but eventually the practice subsided. In the early days of the use of barbiturates there were only slight indications that these drugs might be misused and thus it was decided that additional control of them should await evidence of morbidity and mortality. That evidence was not long in coming and within a few years the problem had reached such a magnitude that the Committee on Public Health deemed it desirable to recommend the imposition of further controls over usage of these drugs.

Of course the important variable in the issue is the nature and degree of any

increase in control. The Committee is of the opinion that the evidence that tranquilizing drugs are now a menace to public health is inconclusive. It believes therefore that there are now no substantial grounds for establishing controls over tranquilizing drugs to such a degree as those over barbiturates.

It is concerned about the possibility of misuse of tranquilizing drugs becoming a danger to public health. Indeed, it is equally or more concerned about the possible misuse of other drugs. As a general principle it believes that all drugs which belong in the category of potentially harmful or new drugs obtainable only upon prescription should be used only under medical supervision. This principle is a sound and self-evident criterion by which to test existing and formulate any new needed regulations and restrictions.

An amendment to the Federal Food, Drug and Cosmetic Act provides that a drug intended for use by man which is a habit-forming drug or a potentially harmful drug or new drug shall be dispensed only upon a written prescription of a licensed practitioner, and refilling is authorized only upon written or oral order of the prescriber of the original prescription. All of the tranquilizing drugs come under these federal provisions; hence they can be obtained only on prescription which cannot be refilled without the order of the original prescriber. But this law does not apply within states unless there is interstate commerce in the drugs.

The Sanitary Code of New York City lists a number of harmful drugs for which a prescription is required. No prohibition against refilling of the prescription is specified except for three categories: sulfonamides, barbiturates and narcotics. Special rigid restrictions apply to the dispensing of barbiturates, particularly in the manner of refilling prescriptions. In the prescribing and dispensing of narcotic drugs, the Code defers to the laws of the State of New York. It is apparent that on the point of refilling of prescriptions for potentially harmful or new drugs, the Code is, with the exceptions noted, in many respects much more lax than the Federal Food, Drug and Cosmetic Act. Consequently it falls short of ensuring medical supervision over the use of these drugs.

The Committee recommends that the Sanitary Code be revised to make it accord more fully with the provisions of the Durham-Humphrey Amendment to the Food, Drug and Cosmetic Act in respect to drugs which shall be available only upon prescription. Under this recommendation such drugs would include: new drugs, potentially harmful drugs and habit-forming drugs. This categorization should supersede the present list of individual drugs specified in the Sanitary Code. It would be more inclusive and at the same time more adaptive to future as well as present contingencies. It should be provided, as at present, that such drugs should be dispensed only upon prescription. The Committee further recommends that the Sanitary Code be revised to provide that prescriptions for potentially harmful drugs and new drugs should not be refillable except upon written or oral order of the original prescriber. As exceptions, it would specifically assert that all existing tighter restrictions on the prescribing and dispensing of barbiturates and narcotic drugs would still prevail and would not be altered by such a proposed revision. This second recommendation would further bring the Sanitary Code much more in accord with the Federal Food, Drug and Cosmetic Act.

It should be noted that prescribing and dispensing of tranquilizing drugs would be covered by these recommendations. Most of all, they would bring the use of potentially harmful and new drugs under full medical supervision.

An additional aspect of the situation is the extravagant and distorted literature

which some of the drug houses are distributing to the medical profession. Such literature may be misleading in two respects. First, it may recommend a product in such a way as to lead to, if not encourage, its indiscriminate use. For example, a leaflet accompanying one tranquilizing drug lists under indications an almost endless number of situations and conditions of emotional stress at every stage of life: hyperactivity, irregular sleeping habits, nightmares and homesickness in children; the various circumstances in adolescence which give rise to severe anxiety and tension; in adulthood, apprehension and anxiety over finances, effects of excitement or misfortune in the family such as sickness, accidents, weddings, funerals, separations, and differing opinions. The drug is also said to be indicated in times of occupational stress: such as, anxiety over interviews, competitive examinations, or public appearances. Thus it is recommended for actors and actresses, radio and television performers, business executives, toastmasters, ministers, teachers, professors and politicians. It is reported to be useful in the journalistic and advertising field with its tension, excitement, and noisy environment. The indications also include competitive sports.

Secondly, some manufacturers' literature which is distributed to physicians and pharmacists contain too frequently little or no mention of side effects and contraindications to the use of the tranquilizers. In one instance it is stated that the drugs are recommended for relatively short-term therapy and temporary conditions where emotional stress is a complicating or a causative factor. Most revealing is the assertion that investigations are under way to determine the safety and efficacy of the drugs during prolonged use. The failure to mention possible side reactions, contraindications and potential dangers, or to devote a disproportionately small space to them, is likely to be highly misleading to the physician.

Manufacturers' literature on new drugs is presumed to guide the physician, not mislead him. Undoubtedly it will color the physician's attitude toward the drug, his use of it and his recommendations concerning it. Ultimately it affects in part the patient's attitude toward and use of the drug. When it is remembered that the physician may obtain his first information about new drugs from this literature, its validity and cautiousness become a matter of high importance.

The lay press has contributed its share to disseminating premature and incomplete accounts of the miraculous effects of the drugs. This practice has had its effect upon the public and ultimately both directly and indirectly upon the medical profession. From such journalism persons may obtain false impressions and exert pressure on their physicians to prescribe the tranquilizing drugs.

Through its Committees on Research, Therapy, and Public Information the American Psychiatric Association has urged avoidance of premature and unreliable reports because they violate the standards for testing new therapies. It advised:

"The full cooperation of the profession in accumulating a body of tested scientific data about the drugs is of prime importance. . . . At the same time it is important to be aware of subtle pressures that combine to foster public misunderstanding and misuse of the drugs. There is the eagerness of the public, and of physicians themselves, for 'good news' about a new treatment for psychiatric disorders. This tends to foster popular stories based on optimistic reports of early and limited research findings with the drugs, before such findings can be reproduced and validated by other colleagues. . . . Persons engaged in any form of research or evaluation of therapy should be most dispassionate and objective in their pronouncements. It is suggested that Members of the Association be particularly alert

to personal pressures (both internal and external) and circumspect in their announcements of early experimental results with the drugs."

The Board of Health is charged with the responsibility of enacting legislation to prevent not only over-the-counter sales and misuse of prescription drugs but also fraudulent or misrepresentative claims or statements about them. Because of the uncritical nature of some of the medical literature sent to physicians by pharmaceutical houses, particularly the expansive, extravagant and indiscriminate listing of indications with inadequate citation of side reactions, contraindications and precautionary measures, the Committee on Public Health recommends that the Board of Health survey this literature as the first step toward bringing about improvement in it so that it may be a more reliable guide to physicians.

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BERNARD SUTRO OPPENHEIMER LECTURE

Dr. Dickinson W. Richards, Lambert Professor of Medicine, College of Physicians and Surgeons, Columbia University and Director of the First Medical (Columbia) Division, Bellevue Hospital, will deliver the first Dr. Bernard Sutro Oppenheimer Lecture on May 21, 1957 at 8:30 p.m. in Hosack Hall of The New York Academy of Medicine, 2 East 103 Street, New York City. The title of Dr. Richards' lecture will be "Some Problems in the Physiology of Dyspnea."

NEW YORK PATHOLOGICAL SOCIETY

ABSTRACTS OF PAPERS AND DISCUSSION

Presented at the Meeting of May 24, 1956, at The New York Academy of Medicine

*Studies with Cancer Cells and Experimental Chemotherapeutic Agents in Tissue Culture**

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Studies in tissue culture of the direct effect of candidate chemotherapeutic agents on neoplastic cells are one part of the broad program in experimental cancer chemotherapy of the Sloan-Kettering Institute for Cancer Research. Differential effects on the growth and integrity of cultured normal and neoplastic cells of the mouse and of man are sought with a variety of agents. Tissue culture screenings of chemicals are supplementary to more extensive testing of agents against transplantable rodent tumors in rats and mice and, of late, against human cancers implanted in cortisone-treated rodents. This work is performed by other sections of the Institute. The interest in tissue culture is not primarily in screening a large number of compounds but in learning more about how selected chemical agents act on neoplastic and normal cells. Tissue culture allows this to be done in the absence of the whole animal with its modifying influences on drug effectiveness.

Under the assumption of possible fundamental metabolic differences between cancer cells and normal cells with respect to growth, we have been using agents expected to interfere in the metabolism of the two classes of cell constituents prominently associated with growth: nucleic acids and proteins. In other words, the agents used belong to the class of counterfeit chemicals called antimetabolites. We have been concerned with the inhibition of growth in tissue culture by antimetabolites and with the alleviation of that inhibition by normal metabolites.

Two methods of tissue culture are used. In the first, fresh explants of mouse sarcoma 180 and of mouse embryo skin are grown in plasma clots on coverslips in roller tubes containing a biological medium of serum and embryo extract. After several days' incubation, the cultures are exposed to the agent in the medium for 24 hours and then observed for effect. In the second method, human cell strains of cancer and normal tissue origin are grown on coverslips without clot in tubes containing a semi-synthetic medium devised by Eagle.[1] This medium, which is completely defined except for 10 per cent of serum, provides a better-understood background against which to carry out studies on antimetabolites.

Cells grown on glass without clot make excellent subjects for recording photographically the effects of chemical agents on structural constituents of cells. Examples are given of living cells photographed through the phase contrast microscope.

* The work presented in this paper was supported by an institutional grant from the American Cancer Society and by research grant C-678 from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service.

Permanent records of experiments with both culture techniques are made by fixing and staining the cells on the coverslips. Mounted, these are used for determining the incidence of mitosis, mitotic aberrations, and dead cells in the cultures under various experimental conditions.

A review of our tissue culture experimentation with 6-substituted purines, analogues of adenine and hypoxanthine, demonstrates the differential susceptibility of different cell types to these antimetabolites. Sarcoma 180 cells are especially sensitive. Different purines have individual toxicities and also cause different effects. Some cause far more mitotic aberrations than others. The toxicity of agents such as 6-mercaptopurine can be blocked with a variety of different physiological substances containing adenine moieties, to different extents with different cell types. Certain physiological substances increase toxicity of the antimetabolites, again to one cell type more than to others.

Making nucleosides of these 6-substituted purines by adding sugars makes a new class of compounds whose activities are not immediately predictable from those of the purines. In general, the 6-substituted purine nucleosides are more toxic than their free purines, and their selectivity of action against different cell types may be radically changed.

Results on human cells in semi-synthetic medium tend to agree with those on mouse cells in biological medium, although the human cells often appear less sensitive.

The 6-substituted purines and their nucleosides are thus seen to form two groups of interesting agents of great diversity in their relative toxicities to the different cell types employed. Attempts to block them with various physiological substances indicate a considerable diversity in the metabolic pathways in which they interfere. These appear to be compounds of considerable potential in experimental cancer chemotherapy.

Tissue culture studies such as these support the notion of a practicable cancer chemotherapy based on the manipulation of biochemical differences between normal and neoplastic cells by means of antimetabolites. Differential responses can be obtained, and these may be accentuated with substances of a second sort. The effect of the latter, which may be normal physiological substances, may be to reduce the toxicity of the inhibitor for one cell type or to increase its toxicity for another. The response of a given cell type to a given inhibitor is determined not only by their respective natures but is also subject to the physiological or biochemical state of the cells as conditioned by their total environment.

DISCUSSION

GEORGE PAPPAS: In your tissue cultures, did you use any of the cellulose sponge techniques?

JOHN J. BIESELE: No.

GEORGE PAPPAS: Just glass and plasma clots?

JOHN J. BIESELE: Yes.

SIGMUND L. WILENS: As a person completely uninformed in the field I am afraid that the question I am about to ask may be very trite. How do you know whether the type of inhibition which you get in tissue culture under your experimental conditions would be in any way comparable to the changes that might occur in tumor cells in their more natural state inside the living animal? Is that an unfair question?

JOHN J. BIESELE: No, I probably have to say I do not know. Our tissue culture studies are on direct effects and try to sidestep complications introduced by the whole organism.

SIGMUND L. WILENS: There are substances like colchicine that do apparently have the same *in vivo* and *in vitro* effects.

JOHN J. BIESELE: Yes, although Dr. Murray has worked far more with that than I have; I believe such substances do have similar effects in culture and in the animal. One might say, if one can protect cells in culture against an antimetabolite with a normal substance, the ability to protect the animal or the tumor cells in the animal against the antimetabolite with the same substance might indicate a similarity of

action in the culture and in the animal. There are some examples of that, although there are some marked failures of correspondence. Dr. Clarke of Sloan-Kettering has tried to protect sarcoma 180 cells in the mouse against 6-mercaptopurine with coenzyme A and has failed to obtain any protection.

QUESTION FROM AUDIENCE: Have you combined purines with folic acid antagonists?

JOHN J. BIESELE: No, I have not; that is a good idea, to work with so-called combination chemotherapy and try to block several different stages in the synthesis of the end-product.

MARGARET R. MURRAY: If I may, I would like to comment on the question before the last one, about a correlation between the effects *in vivo* and *in vitro*. I have had just a little experience there, in that we have tried in the last couple of years to correlate the effect of a spectrum of antimetabolites and inhibitors on a mouse glioma in culture, a human glioblastoma in culture, in animals bearing the mouse glioma, and clinically in humans. To date it would seem that the correlation between the mouse tissue cultures of the brain tumor and the human tissue cultures of these brain tumors is better than the correlation between tissue cultures and the mouse or human *in vivo*. This has applied to a good many inhibitors, but every now and then we have found an antimetabolite that was effective both in tissue cultures and in the mouse *in vivo;* then we proceeded to try it on the human. In the gliomas one of our major problems seems to be to introduce the compound into the tumor tissue *in vivo* in a concentration comparable to the lethal level *in vitro*.

JOHN J. BIESELE: The problem of correlation between results in culture and in the animal was discussed in a paper before the New York Academy of Sciences. Representatives of a number of classes of inhibitors were used, and it was found that the correlation of results may present a different problem with each new class of inhibitors. With purines, mitotic inhibition in culture gives a reasonable indication of activity *in vivo*. Too much reliance should not be placed on tissue culture results alone in chemotherapeutic screening.[2]

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Some Uses of Tissue Culture in the Classification and Diagnosis of Human Tumors

MARGARET R. MURRAY and ARTHUR PURDY STOUT

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It is well known that the fixed cells of the body when transplanted into tissue culture conditions often undergo changes in morphology. These changes, which may be of considerable magnitude, represent the cell's response to an altered environment—one which differs chemically to some degree from that afforded by the parent organism, and differs even more importantly in aspects that might be called physical or mechanical. There is less crowding: the cells are at liberty to wander some distance into the surrounding medium: freed by the excision from stromal sheaths and other mechanical impediment, and attracted by pH and nutrient gradients, they migrate out of the explant along whatever substrate is afforded. The early tissue culture workers were astonished and then absorbed by this vagrant proclivity of the so-called fixed or noble cells. Since then a whole science of cell dynamics has grown up, and now it is the fashion to inquire what it is that holds the *body* cells in leash and keeps them more or less quietly where they belong.

For our purposes these studies in cell dynamics have resulted in the demonstration that each cell type has a repertory of reversible changes in form, or "modulations" (Bloom, 1937,[1] Weiss, 1939[2]), which it displays in culture, and by which under favorable circumstances it may be recognized. Normal adult tissues—a notable example is skeletal muscle—may assume *in vitro* a variety of forms not encountered *in vivo*, but observable in the embryonic, regenerative or neoplastic state. This whole morphologic spectrum may overlap that of other tissue types to greater or lesser degree and yet be as a whole distinctive: a disease syndrome is a good analogy here.

Human tumors, like normal tissues explanted *in vitro*, have their quota of modulations and these may coincide rather closely with the spectrum that characterizes their normal tissue types. Consequently the behavior of tumor cells in culture may reveal new information that is not discernible in the sections, and it may be crucial for their classification as to tissue of origin. Intrinsic tissue characteristics are sometimes emphasized in the new environment of the culture, where the migrating cells are freed from the compression to which they are subject *in vivo*, and where the cell can always be seen in its entirety, as well as the patterns typically formed by groups of cells (Murray and Stout, 1954[3]).

Basically, our method has been to compare the cultural characteristics of the tumor type in question with those of the normal tissues with which it might be thought to be related. Thus, neurilemmomas were compared *in vitro* with fetal and adult Schwann cells and with endo-perineurium (Murray and Stout, 1940, 1942[4, 5]). This kind of study requires that the tissue not be stimulated to rapid reproduction, but be fed little more than a maintenance ration, and be persuaded in various ways to expend its energy in differentiating. To this end, in most of our work we have used the Maximow double-coverslip well-slide method, carrying cultures from a fortnight to a month in a plasma clot, without transfer (Murray, 1951[6]). The possibilities of inducing tissue organization *in vitro* can be further extended by the watch-glass method of organ culture (Fell, 1951[7]), and by the Leighton tube method (Leighton, 1951[8]), which makes use of a fine-pored cellulose sponge into which the cells infiltrate; but these preparations have the disadvantage of being too thick for transillumination, thus cannot be examined satisfactorily while living, and must be sectioned like the original tumor block. Their chief advantage is realized with epithelial tissues, which in the coverslip-cultures tend to revert to a relatively undifferentiated squamous type of

growth, and to lose their topographical relationships, which are of diagnostic value in the classic pathologic sections. In sponge and watch-glass cultures epithelial tissues find a more congenial substrate, which permits them to organize into acinar or other structures. The significance of mitotic index as a gauge of malignancy is reduced *in vitro*, since normal adult cells ordinarily show a modicum of division in culture.

In nerve tissues, however, distinguishing cellular characteristics are generally intensified by cultivation *in vitro*. The most obvious advantage of the roomier culture environment is to allow the projection and expansion of cell processes, which, in the case of the neuron, are immediately recognizable. This has led to the use of tissue culture as the quickest, as well as the most certain means of diagnosing the sympathicoblastoma (Murray and Stout, 1947[9]). Supporting cells also, such as the Schwann cell, oligodendroblast and astroblast, assume much more distinctive forms *in vitro* than can be seen in sections, either normal or neoplastic.

For our purpose the mesoblastic tissues in general occupy an intermediate position between those of nervous derivation and the covering and lining epithelia. For most mesoblastic tumors tissue culture is best used as a diagnostic aid in conjunction with clinical and routine pathologic observations; it may provide a means of deciding among several alternatives left open by those methods—for example, the choice between liposarcoma, rhabdomyosarcoma and fibrosarcoma or myxoma (Pack and Arciel[10]). A mesothelioma may be detected by this means (Stout and Murray, 1942[11]), or distinctions made among lymphomas (Murray and Stout, 1954[3]). The behavior of Hodgkin's nodes in culture aligns them rather with the inflammatory lymphomas than with the lymphosarcomas, and may therefore afford a clue to the Hodgkin's etiology.

Observations *in vitro* on an infiltrating glomus tumor of the ankle region have led us to classify the "epithelioid cell" of the neuro-myo-arterial glomus as a derivative of the capillary pericyte (Murray and Stout, 1942[12]), and to establish a new tumor grouping, the hemangiopericytoma (Stout[13]).

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DISCUSSION

JOHN G. KIDD: May I ask Dr. Murray whether she has attempted serial transfer of the lymphomas?

MARGARET R. MURRAY: By serial transfer, you mean through eggs?

JOHN G. KIDD: Repeated subcultures.

MARGARET R. MURRAY: No, we have not done that. Our whole system depends on carrying them *in vitro* for a short time and picking up what we can before they have a chance to be modified.

SIGMUND L. WILENS: Dr. Stout implies that the tissue culture technique is probably not applicable for surgical pathologic diagnosis. That is disappointing to surgical pathologists who have to make difficult diagnoses. I notice, however, in the

case of sympathicoblastoma you were able to demonstrate the growth of neurofibrils in 24 to 48 hours. This is rapid enough to be useful diagnostically. What are some of the time periods required of other tumors in tissue cultures to make a definite diagnosis?

MARGARET R. MURRAY: We like to wait about a week for most types, and sometimes it is a good deal longer before we can come up with a diagnosis. In the matter of making a differential diagnosis of Hodgkin's lymph nodes, I think I made some errors in the beginning, from overenthusiasm, because I happened to have a series in which I could pick up the characteristic Hodgkin's cells in 48 hours. That does not always hold. The sympathicoblastoma is the one case in which we can really expect to make the diagnosis quickly.

SIGMUND L. WILENS: Dr. Stout, do you think that every well organized surgical pathology department ought to have a tissue culture division?

ARTHUR PURDY STOUT: Not unless the one who is going to run it is extremely well provided with funds, and he or she is a Dr. Murray, or has a Dr. Murray handy to interpret these things. We do not want you to go away with the idea that it is easy to recognize the way these different cells grow. Dr. Murray made it seem very rapid and very simple on the slides she showed you, but just try it some time!

JOHN G. KIDD: This is a discussion of both of this evening's papers. Essentially what I should like to do is to commend Dr. Biesele and Dr. Murray not only for the papers they have presented and the precise results they have shown, but also for the implications which their findings hold for cellular biology and cellular pathology. Not so long ago a distinguished British biologist, in a review having to do with cellular differentiation, asked himself a rhetorical question and immediately provided the answer. The question was, "Where would biology be today if the method of tissue culture had never been devised"; the answer was, "Where biology is." This cynical statement had hardly come off the press when events took an unpredictable upturn, and they have, I think, been taking further upturns ever since. For example, Dr. Enders in Boston soon thereafter showed that poliomyelitis virus would grow in extraneural tissues cultured *in vitro*. Think what this discovery has meant to biology and to pathology. It has not only provided a method whereby a practical vaccine has been made, but it has greatly influenced our ideas about the pathogenesis of poliomyelitis. We now know that the viruses of infantile paralysis can proliferate in tissues other than the nervous system, and we can now focus our attention on the viremia and on the proliferation of the viruses in the nasopharynx and in the gastrointestinal tract to the further benefit of our knowledge about the pathogenesis of the disease. This evening Dr. Biesele has shown how competition between the effects of metabolites and antimetabolites can be used as a means of distinguishing subtle differences between normal and neoplastic cells, and Dr. Murray has pointed to the divergent differentiation exhibited by cells presumably of a single type, cultured *in vitro*, and furthermore she has coined the rather elegant term "morphological modulation" to describe this phenomenon. It seems to me not too venturesome to think—in view of the work of Philip White and Harry Eagle and George Gey and many others—that we may in the not too distant future be able to grow mammalian tissue cells in liquid media in the laboratory in much the way we today grow *E. coli* in broth. Certainly in the foreseeable future we shall probably see a greatly extended utilization of this method, and perhaps it will become possible for ordinary mortals, who are devoid of the special capabilities that Dr. Biesele and Dr. Murray possess, to employ this method, and with it to learn more about how cells behave under normal and abnormal conditions.

DR. BETTY ELLIS ARONSON: I should like to ask Dr. Murray what media she employs? Did she use something to maintain cell growth?

MARGARET R. MURRAY: Our standard medium was three parts human placental serum, one part chicken embryo extract, and one part beef serum ultrafiltrate. Clotted chicken plasma provides the original substrate.

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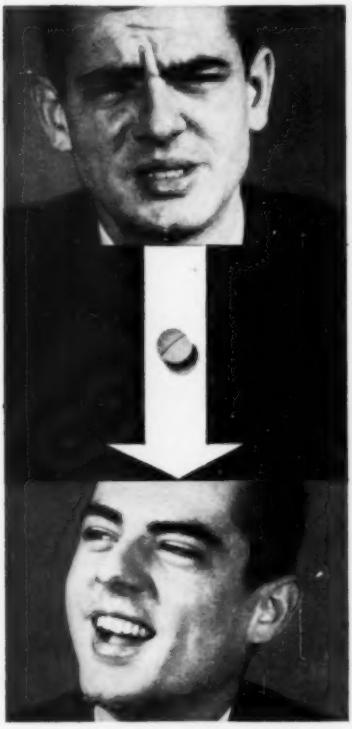

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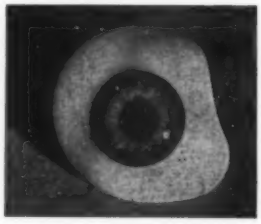

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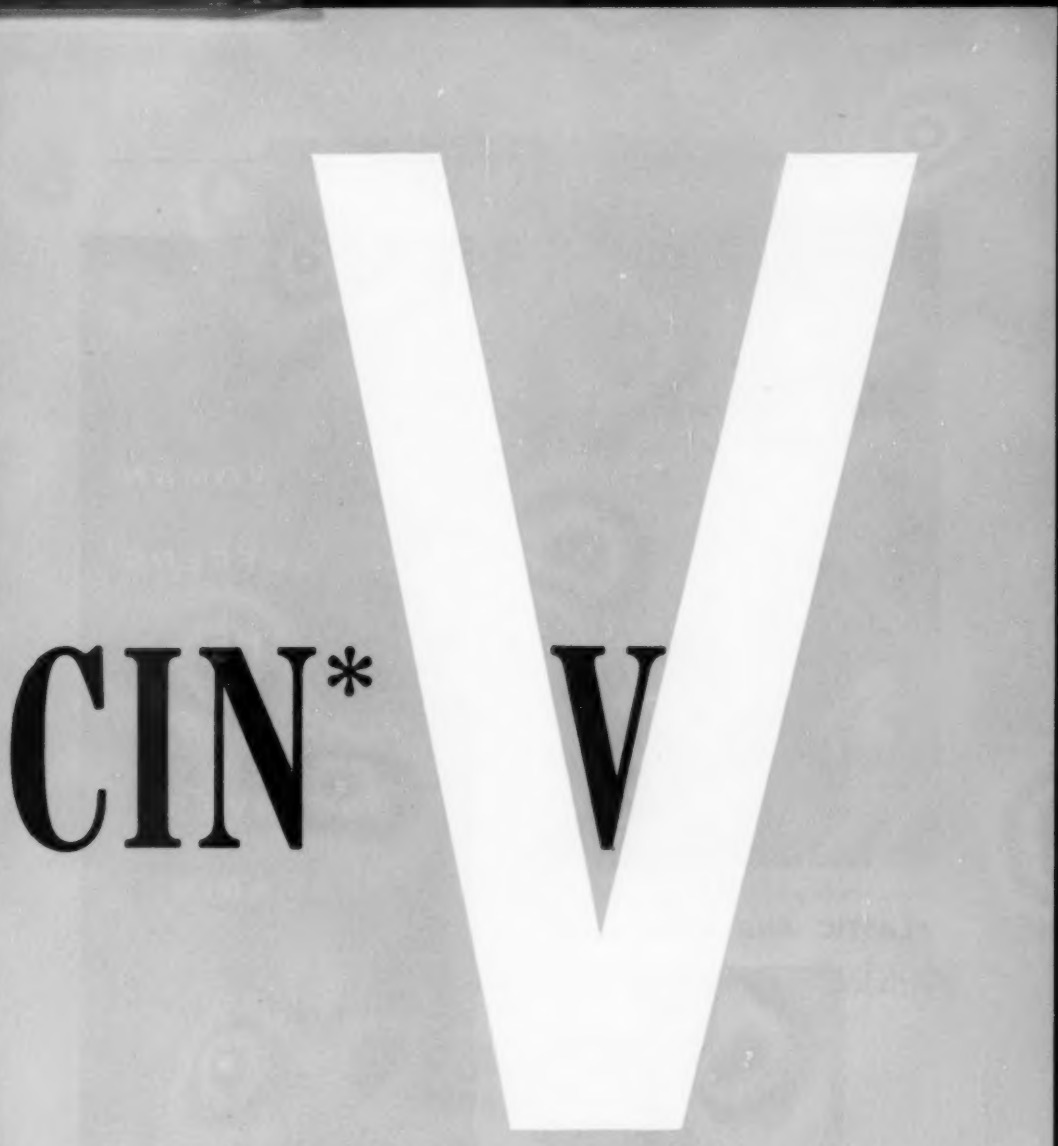

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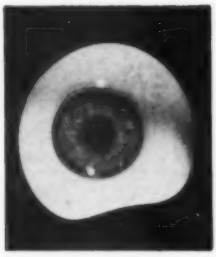

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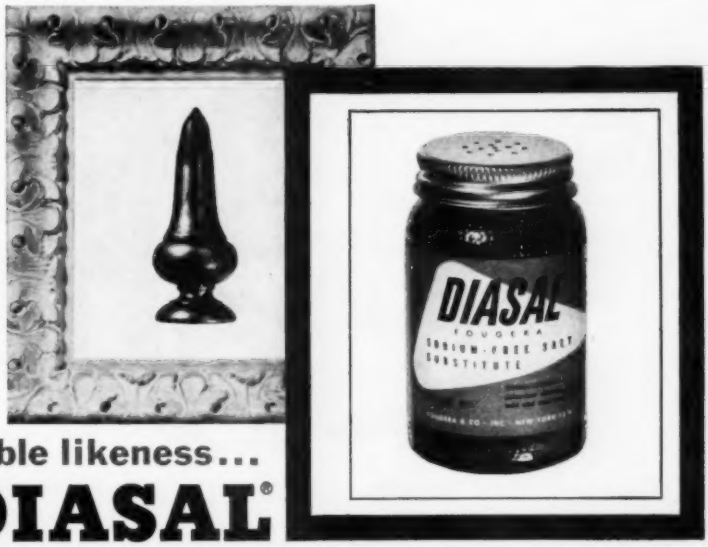

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April 4 — CORTISONE AND RHEUMATOID ARTHRITIS — John J. R. Duthie, *Midlothian, Scotland.*

FREUD AND PROPHYLAXIS — Paul V. Lemkau, *Director, New York City Community Mental Health Board, New York.*

April 11 — VASCULAR SURGERY — Professor Sir James Paterson Ross, *St. Bartholomew's Hospital, London, England.*

FREUD'S INFLUENCE IN CONTEMPORARY CULTURE — Iago Galdston, *Executive Secretary, Bureau of Medical Information, New York Academy of Medicine, New York.*

April 18 — ANAEMIA — Professor Leslie J. Witts, *Oxford, England.*

THE BIOSYNTHESIS OF ADRENAL CORTICAL HORMONES—Gregory Pincus, Sc.D., *Research Director, Worcester Foundation for Experimental Biology, Shrewsbury, Massachusetts.*

April 25 — SURGERY, RADIOTHERAPY AND CHEMOTHERAPY OF ADVANCED MALIGNANT DISEASE — Professor Brian W. Windeyer, *Meyerstein Institute of Radiotherapy, Middlesex Hospital, London, England.*

GALENICALS AND GALENISM IN THE HISTORY OF MEDICINE — Owsei Temkin, *Associate Professor of the History of Medicine, The Johns Hopkins University School of Medicine, Baltimore, Maryland.*

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1. Hardin, J. H.; Levy, J. S., and Seager, L.: South. M. J. 47:1190,1954.

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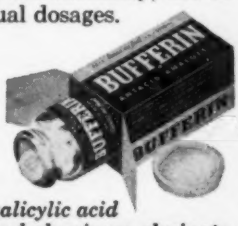

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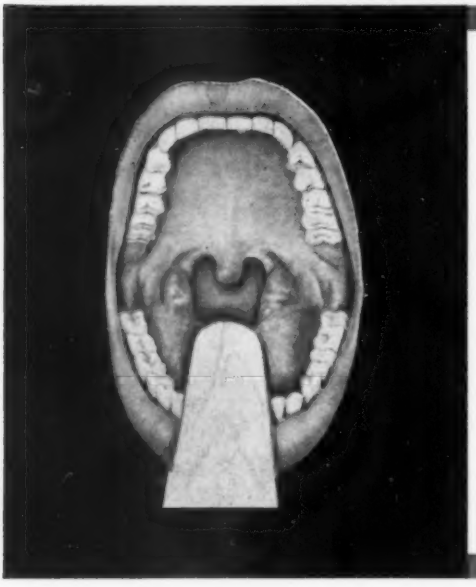

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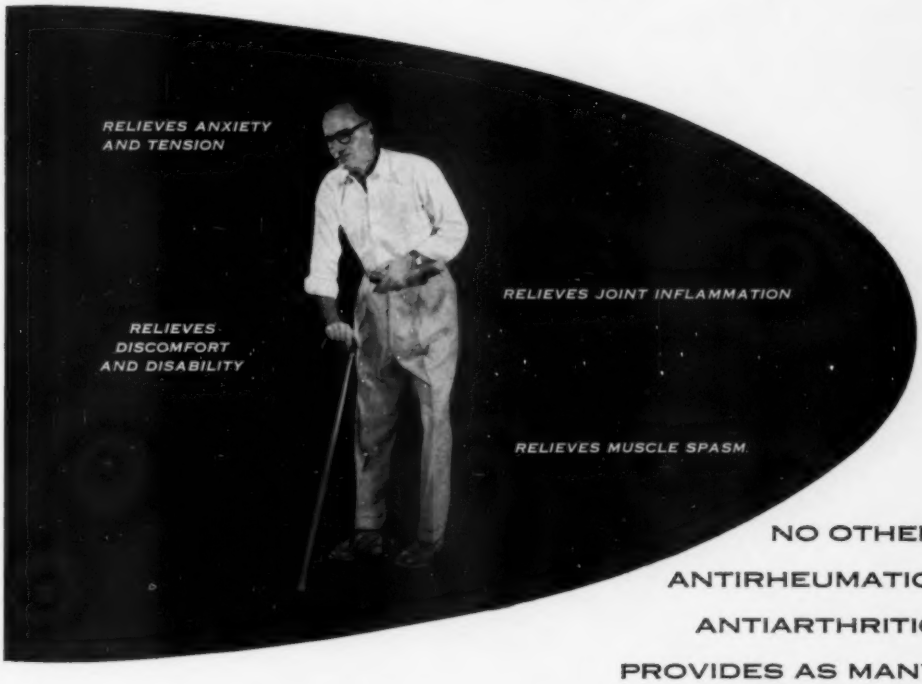
1. Carter, C. H., and Maley, M. C.: Antibiotics Annual 1956-1957, New York, Medical Encyclopedia, Inc., 1957, p. 51.



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